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Design and Synthesis of Novel Molecular Scaffolds of Bicaultamide Derivatives for the Treatment of Prostate Cell Cancer

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ABSTRACT

Prostate cancer is a major cause of male death worldwide and the identification of new efficient treatments is constantly needed. Different non-steroidal androgen receptor antagonists are approved also in the case of castration-resistant cancer forms. Using a rational approach and molecular modelling studies to modify the structure of antiandrogen drug bicalutamide, a new series of phenylsulfonyl-benzamide derivatives was designed and synthesised. Their antiproliferative activities were evaluated in four different human prostate cancer cell lines and several new compounds showed significantly improved IC50 values in the low μM range. The cytotoxicity profile was also evaluated for the novel structures in the HEK293 cell line.

Keywords : Bicaultamide, Prostate Cell Cancer, IC50, HEK293, Prostate cancer, CRPC

I. INTRODUCTION

Prostate cancer (PC) is one of the major causes of male death worldwide, representing the second most common cancer in males.[1] Prostate cancer is a major cause of male death worldwide and the identification of new efficient treatments is constantly needed. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases (759,000) occurring in more developed regions.

Prostate cancer is the development of cancer in the prostate, a gland in the male reproductive system. Most prostate cancers are slow growing; however, some grow relatively quickly[2]. The cancer cells may spread from the prostate to other area of the body, particularly the bones and lymph nodes.

PC cell growth is strongly dependent on androgens, therefore blocking their effect can be beneficial to the patient's health. Such outcomes can be achieved by antagonism of the androgen receptor (AR) using anti-androgen drugs, which have been extensively explored either alone or in combination with castration [3](**1**), Flutamide (**2**) hydroxyflutamide (3), bicalutamide (4), Enzalutamide (5), Curcumin (6), nilutamide (7) and RU56279 (8) are all non-steroidal androgen receptor antagonists (AR) approved for the treatment of PC.

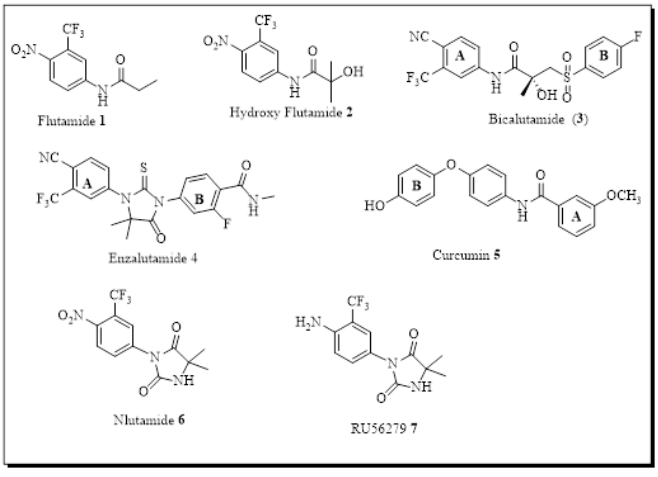


Figure 1 : Structures of various anti androgens used currently for the treatment of prostate cancer

In many cases, after extended treatment over several years, these anti-androgens become ineffective and the disease may progress to a more aggressive and lethal form, known as castration resistant prostate cancer (CRPC). The major cause of this progressive disease is the emergence of different mutations on the AR, which cause the anti-androgen compounds to function as agonists, making them tumour-stimulating agents [4]

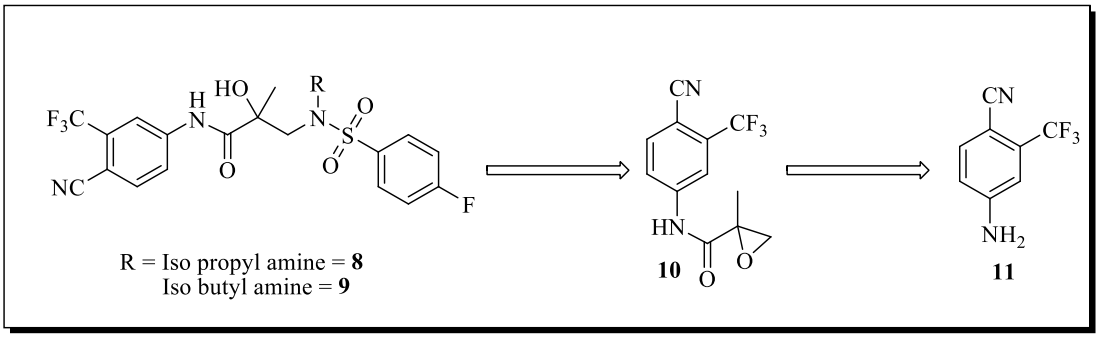
Among the drugs used for the treatment of PC, bicalutamide and enzalutamide selectively block the action of androgens while presenting fewer side effects in comparison with other AR antagonists[5-6]. Non-steroidal ligands are more favorable for clinical applications because of the lack of cross reactivity with other steroid receptors and improved oral bioavailability. Among them, Bicalutamide is the most potent and tolerated drug of choice administered either as monotherapy o8ikl\r with adjuvant castration or luteinizing hormone-releasing hormone.

Structurally these are comprised of two differently substituted aromatic rings, named ring A and ring B, connected by a linker, either linear (Bicalutamide-like compounds) or cyclic Enzalutamide (like compounds), recently, a novel 4-(4-benzoylaminophenoxy) phenol anti-androgen scaffold, derived from the natural pigment Curcumin, has been reported, in which a central phenyl group is acting as linker connecting two different aromatic rings.

One of the most common mutations found for bicalutamide is W741L in helix 12 of the receptor,[7] which allows the protein to adopt its closed agonist conformation even in the presence of the antagonist: with this mutation, due to some residual structural flexibility in 1, ring B can bend to occupy an inner portion of the ligand-binding domain, thus allowing the closure of the receptor into its agonist conformation. Treatment with enzalutamide induces instead a F876L mutation in the AR, which also confers an antagonist to agonist switch in activity for the drug.[8] Second generation antiandrogen ARN-509 (Fig. 1), which is now in Phase III clinical trials.[9]
However it was reported recently that these anti-androgens tend to become ineffective due to adaptive mutations on the structure of the androgen receptor, which renders them agonistic.

II. METHODS AND MATERIAL

In the present chapter we reported the design and synthesis of novel molecular scaffolds of Bicaultamide, wherein the steric strain in the linker is increased by derivatisation of secondary amine as illustrated in **Scheme 1**. The retrosynthetic analysis illustrates the synthesis of N-substituted sulphonamidesfrom substituted aromatic amines.Aromatic amines on condensation with methacrolyl chloride, followed by epoxidation and aminolysis with aliphatic amines yielded the amino alcohols. Further sulphonylation with aromatic sulphonyl chlorides gave novel analogues of Bicalutamide. Similar synthesis was repeated with secondary benzyl amines as starting materials. All the compounds were characterized by, IR, mass, 1H and 13 C NMR and then screened for biological activity against anti-cancer cell lines.

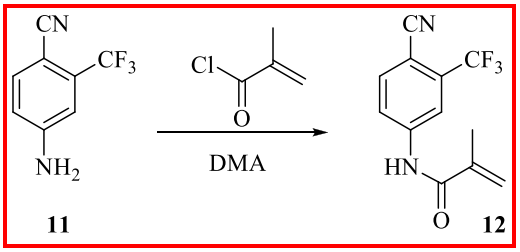


Scheme 1: Retrosynthetic analysis of N-Substituted analogues of Bicalutamide from aromatic amines

In the present chapter we reported the design and synthesis of novel molecular scaffolds of Bicaultamide for biological evaluation

Accordingly the substituted phenyl amine **11** was treated with commercially available methyl acrolyl chloride in DMA for 30 min to give substituted amide **12** in 66.8 % yield.

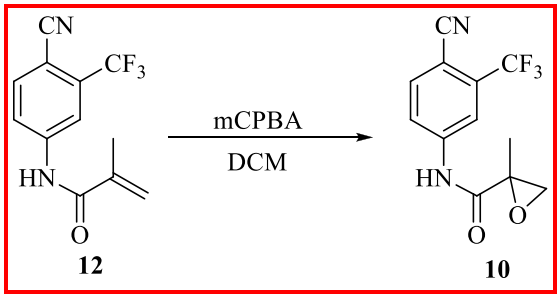
Scheme 2:



In the ^{1}H NMR of **12** signals corresponding to newly introduced olefin group resonated at 5.79-5.74 ppm as a multiplet and the methyl group at 1.98 ppm as a singlet and rest of the protons resonated at expected chemical shifts indicated the methyl acrolyl amide formation. ES1-MS:*m/z* found 277.32 $(M+Na)^+$ gave further confirmation for the stucture of **12**.

The methyl acrolyl amide **12** on treatment with m-chloro perbenzoic acid in CH_2Cl_2 at 0 ^oC for 4 h, yielded the corresponding racemic epoxide mixture **10** in 58.8% yield.

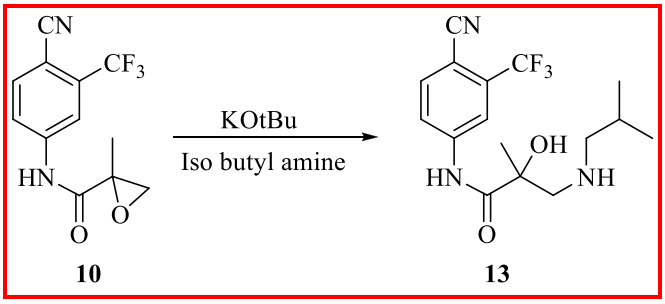
Scheme 3:



The epoxide was confirmed by the loss of olefinic protons at 5.79-5.74 ppm and presence of terminal epoxide protons at 2.96-2.66 ppm appear in the ^{1}H NMR and ESI-MS: m/z found 271.02 (M+H)+ further confirmed the product.

The opening of epoxide **10** in base condition epoxide **10** on treatment with isobutyl amine in presence of a potassium *tert*-butoxide in reflux for 3 h, gave the N-alkyl 1,2-amino alcohol **13** in 71.4% yield.

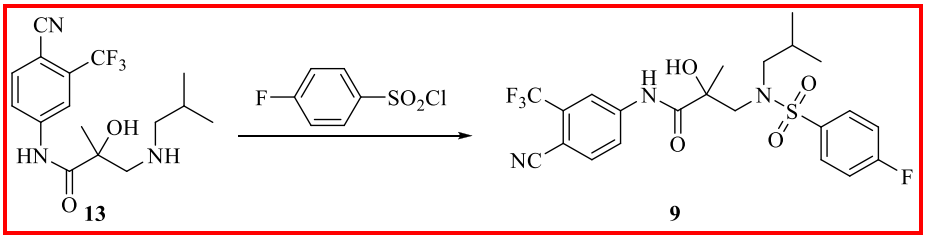
Scheme 4:



In the ^{1}H NMR of **13** the signals corresponding to the isobutyl group appeared at 1.63-1.59 ppm and 0.92-0.89 ppm respectively and ESI-MS: m/z found 344.12 (M+H)+ further confirmed the product.

The N-alkyl 1,2-amino alcohol **13** which were further converted to the p-fluoro sulphonamide **9** on reaction with sulphonyl chloride in CH_2Cl_2 at 0 °C for 6h in 54% yield.

Scheme 5:

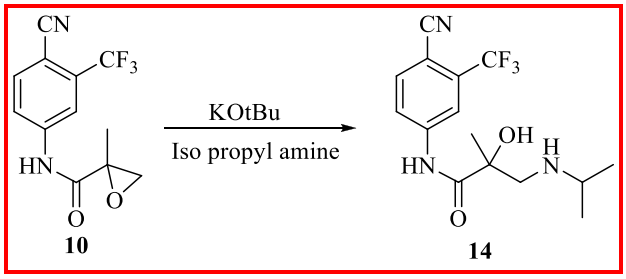


The ^{1}H NMR of **9** the signals corresponding to the newly introduced aromaticgroup appeared at 7.8-7.3 ppm and ESI-MS: m/z found at 524.12 (M+Na)+ confirmed the sulphonamide.

To understand the role of the alkyl chain attached to the amine we prepared various analogues wherein the isobutyl chain was replaced with isopropyl chain. Thus the epoxide mixture **10** on ammonolysis with isopropyl amine in the presence of base i.e potassium tert-butoxide gave the N-isopropyl 1,2-amino alcohols **14** in 70.0 % yield, with loss of epoxide protons at 2.96-2.66 ppm. The amino alcohols on treatment with sulphonyl chloride were converted into sulphonamide **8** in 58.0 % yield.

The opening of epoxide **10** in base condition epoxide on treatment with isopropyl amine in presence of a potassium *tert*-butoxide in reflux for 3 h, gave the N-alkyl 1,2-amino alcohol **14** in 70.0% yield.

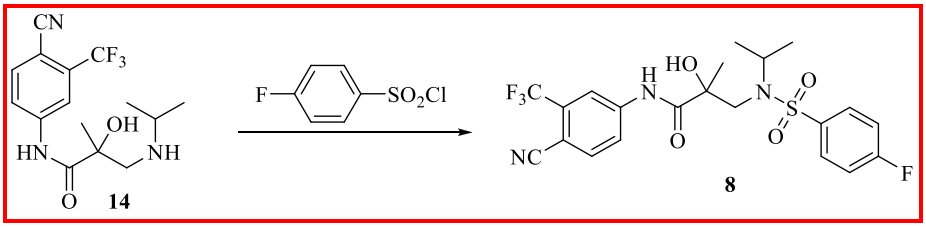
Scheme 6:



In the ^{1}H NMR of **14** the signals corresponding to the isopropyl group appeared at 1.11-0.98 ppm and 2.85-2.83 ppm respectively and ESI-MS: m/z found 330.11 (M+H)+ further confirmed the product.

The N-alkyl 1,2-amino alcohol **14** which were further converted to the p-fluoro sulphonamide **8**, on reaction with sulphonyl chloride in CH_2Cl_2 at 0 °C for 6h in 58% yield.

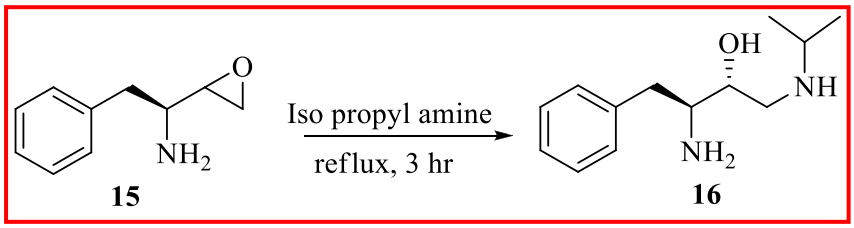
Scheme 7:



The ^{1}H NMR of **8** the signals corresponding to the newly introduced aromaticgroup appeared at 7.6-7.3 ppm and ESI-MS: m/z found at 510.28 (M+Na)+ confirmed the sulphonamide.

The opening of epoxide **15** in base condition epoxide on treatment with isopropyl amine in presence of a potassium *tert*-butoxide in reflux for 3 h, gave the N-alkyl 1,2-amino alcohol **16** in 60.3 % yield.

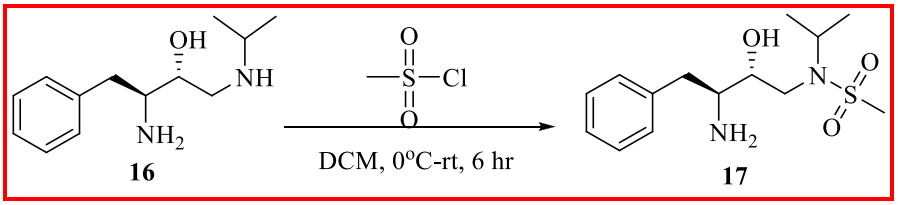
Scheme 8:



In the ^{1}H NMR of **16** the signals corresponding to the isopropyl group appeared at 2.43-2.36 ppm and 0.94-0.91 ppm respectively and ESI-MS: m/z found 223.23 (M+H)+ further confirmed the product.

The N-alkyl 1,2-amino alcohol **16** which were further converted to the methane sulphonamide **17** on reaction with methyl sulphonyl chloride in CH_2Cl_2 at 0 °C for 6h in 53.33% yield.

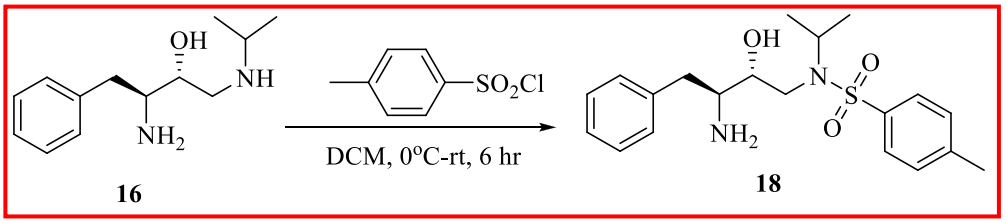
Scheme 9:



The ^{1}H NMR of **17** the signals corresponding to the newly introduced methyl group appeared at 3.03 ppm and ESI-MS: m/z found at 301.22 (M+H)+ confirmed the methane sulphonamide.

The N-alkyl 1,2-amino alcohol **16** which were further converted to the p-methyl sulphonamide **18** on reaction with sulphonyl chloride in CH_2Cl_2 at 0 °C for 6h in 82.0% yield.

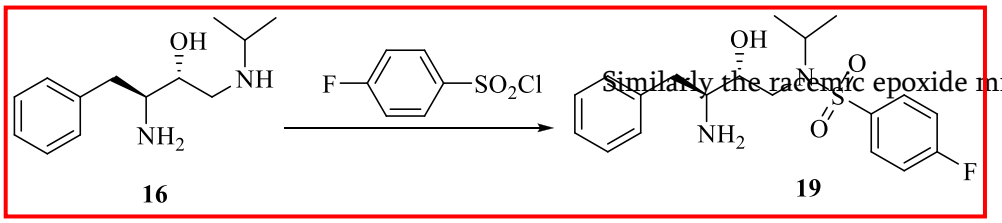
Scheme 10:



In the ^{1}H NMR of **18** the signals corresponding to the p-methyl group appeared at 3.88 ppm and 0.92-0.89 ppm respectively and ESI-MS: m/z found 399.02 (M+Na)+ further confirmed the product.

The N-alkyl 1,2-amino alcohol **16** which were further converted to the p-fluoro sulphonamide **19** on reaction with sulphonyl chloride in CH_2Cl_2 at 0 °C for 6h in 65.5% yield.

Scheme 11:



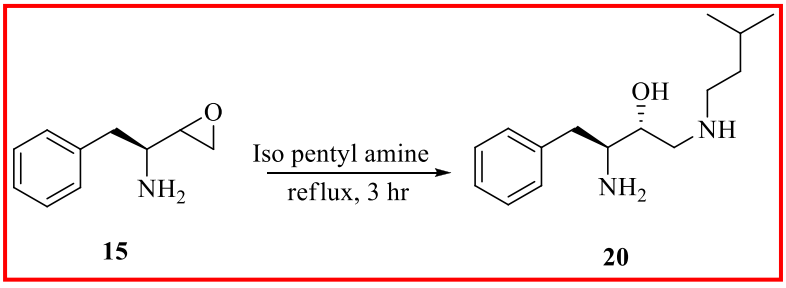
Similarly the racemic epoxide mixture on treatment

In the ^{1}H NMR of **19** the signals corresponding to the aromatic group appeared at 7.87-7.82 ppm and 7.44-7.38 ppm respectively and ESI-MS: m/z found 403.35 (M+Na)+ further confirmed the product.

In the next design we relieved the steric strain in the phenyl ring attached to the amine by removing the methyl group. Thus the racemic epoxide mixture **15** on treatment with isopentyl amine in the presence of potassium tert-butoxidein THF in reflux gave the corresponding 1,2-amino alcohol which was converted to the corresponding sulphonamides 21, 22 and 23 on treatment with methane sulphonyl chloride, p-methyl and p-fluoro sulphonyl chloride respectively in 57.3 %, 62.8 % and 49.7 % yields. These sulphonamides were further confirmed by mass and NMR respectively.

The opening of epoxide **15** in base condition epoxide on treatment with isopentyl amine in presence of a potassium *tert*-butoxide in reflux for 3 h, gave the N-alkyl 1,2-amino alcohol **20** in 78.0% yield.

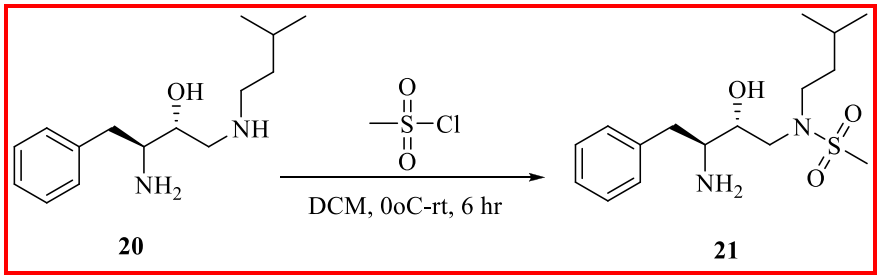
Scheme 12:



In the ^{1}H NMR of **20** the epoxy protons are disappeared and newly formation of corresponding to the isopropyl group appeared at 0.89-0.71 ppm respectively and ESI-MS: m/z found 251.25 (M+H)+ further confirmed the product.

The N-alkyl 1,2-amino alcohol **20** which were further converted to the N-methyl sulphonamide **21** on reaction with methane sulphonyl chloride in CH_2Cl_2 at 0 °C for 6h in 57.3 % yield.

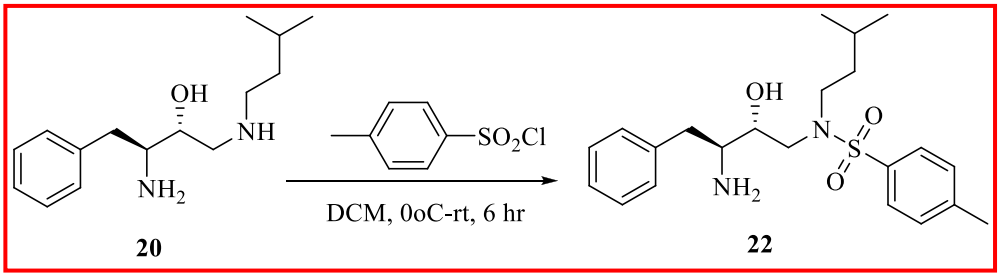
Scheme 13:



The ^{1}H NMR of **21** the signals corresponding to the newly introduced sulphonyl methyl group appeared at 3.03 ppm and ESI-MS: m/z found at 329.14 (M+H)+ confirmed the sulphonamide.

The N-alkyl 1,2-amino alcohol **20** which were further converted to the p-methyl sulphonamide **22** on reaction with sulphonyl chloride in CH_2Cl_2 at 0 °C for 6h in 62.8% yield.

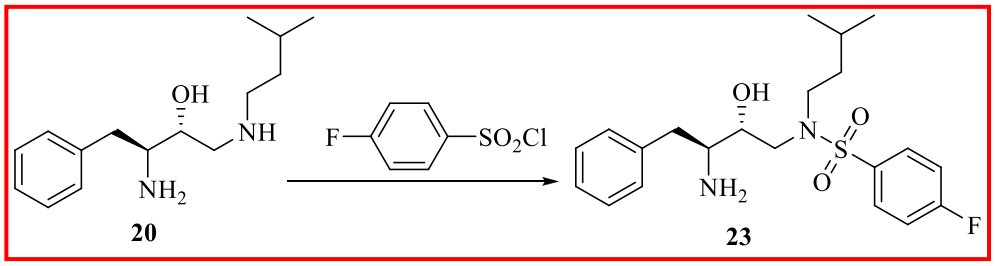
Scheme 14:



The ^{1}H NMR of **22** the signals corresponding to the newly introduced aromatic group appeared two set of proton signal at 7.64-7.61 ppm and 7.39-7.36 ppm. The mass spectrum ESI-MS: m/z found at 405.32 (M+H)+ confirmed the sulphonamide.

The N-alkyl 1,2-amino alcohol **20** which were further converted to the p-fluoro sulphonamide **23**, on reaction with sulphonyl chloride in CH_2Cl_2 at 0 °C for 6h in 49.7% yield.

Scheme 15:

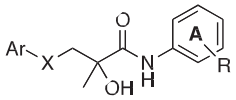


The ^{1}H NMR of **23** the signals corresponding to the newly introduced aromatic group appeared at 7.85-7.80 and 7.44-7.38 ppm and ESI-MS: m/z found at 409.42 (M+H)+ confirmed the sulphonamide.

Results:

MTTassay;

All the compound shave been tested at 8 different concentrations.*MEC: minimum effective concentration that sign I ficantly cross es vehicle control threshold ;**AC50: concentration at which 50% of maximum effect is observed;*** Geometricmean.



Compound	Ar(Bring)	X	R(Aring)	MTTtest		Antiproliferativedata
				MEC(mM)*	AC50(mM)**	Abs.IC50(mM)***
45a(R-	4-F-Ph	SO2	4-CN,3-	19.2	54.3	47.05
44e(*S*-	4-CN-Ph	O	4-CN,3-	21.8	32.8	27.41
22c	3-CF3-Ph	S	4-CN,3-	18.4	36.6	7.23
22d	2-CF3-Ph	S	4-CN,3-	14.7	25.8	6.16
23c	3-CF3-Ph	S	4-NO2,3-	13.2	26.1	7.04
23d	2-CF3-Ph	S	4-NO2,3-	1.71	2.73	5.17
27b	4-CF3-Ph	O	4-CN,3-	11.3	23.9	9.15
28m	4-CN,2-	O	4-NO2,3-	10.6	20.2	6.71
33d	2-CF3-Ph	SO2	4-NO2,3-	22.7	32.6	26.50
42b	4-CF3-Ph	S	4-CN,3-	49.6	61.2	12.24
42c	3-CF3-Ph	S	4-CN,3-CF3	26.6	34.6	13.43

Discussion and conclusion:

In the present chapter we reported the design and synthesis of novel molecular scaffolds of Bicaultamide, wherein the steric strain in the linker is increased by derivatisation of secondary amine as illustrated in **Scheme 1**. The retrosynthetic analysis illustrates the synthesis of N-substituted sulphonamidesfrom substituted aromatic amines.Aromatic amines on condensation with methacrolyl chloride, followed by epoxidation and aminolysis with aliphatic amines yielded the amino alcohols. Further sulphonylation with aromatic sulphonyl chlorides gave novel analogues of Bicalutamide. Similar synthesis was repeated with secondary benzyl amines as starting materials. All the compounds were characterized by, IR, mass, 1H and 13 C NMR and then screened for biological activity against anti-cancer cell lines.

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