Synthesis and Characterization of Some Bioactive *β*-Amino Alcohol Derivatives

A dissertation submitted to Department of Chemistry, Quaid-i-Azam University, Islamabad, in partial fulfilment of the requirement forthe

Degree of

Master of Philosophy

In

Organic Chemistry

By

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Islamabad, Pakistan

2015

In the name of Allah, the Most Merciful, the Most Kind

DECLARATION

This is to certify that this dissertation entitled ***"Synthesis and Characterization of Some Bioactive β-Amino Alcohol Derivatives''*** submitted by ***Miss Maria Bibi*** is accepted in its present form by the Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan, as satisfying the dissertation requirements for the degree of ***Master of Philosophy*** *in* ***Chemistry.***

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Saying of Quran

''Allah will exalt those who believe among you and those who have knowledge to high ranks''

Reported by Hasan bin `Ali (RA):

The Messenger of Allah (peace be upon him) said:

"Give up what is doubtful to you for that which is not doubtful; for truth is peace of mind and False hood is doubt".

“Tirmidhi”

DEDICATION

Dedicated this humble effort to

My Loving Grand Mother (late)

My Parents

My sisters

And

My Whole Family

Whose prayers, affections and love are the source
of strength
and
Sign of success for my life

Specially Dedicated to My Aunt (late)

Whose affections and her wishes for my higher studies
always motivated me for hard work

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First and foremost, I thank Allah (subhana wa taala) for endowing me health, patience, and knowledge to complete this work. Peace and blessings of Allah almighty be upon the Holy Prophet, Hazrat Muhammad (Salal La Ho Alaihey Wassalam) who exhorted his followers to seek for knowledge from cradle to grave.

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My parents deserve my whole hearted thanks as well for their sacrifices, efforts and endless prayers. Especial thanks to my brother Dr.Abdurrahim and my sisters Muslima, Dr. Basanara and Rozina for their support and encouragement.

Maria Bibi

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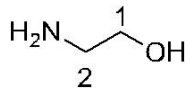
Abstract

A series of new Schiff base derivatives of β-amino alcohols have been synthesized in good yields. The core structure of this series is 1-(2-hydroxy-3-(naphthalene-2-yloxy) propyl) isatin, which has been synthesized via ring opening reaction of naphthyloxy methyl oxirane intermediate with isatin (as nucleophile). The naphthyloxy methyl oxirane intermediate in turn was obtained by nucleophilic substitution reaction of naphthol with epichlorohydrin in presence of strong base. All the synthesized compounds were characterized by their physical and spectral (NMR) data and are expected to have good medicinal properties.

1.1 *β*-Amino Alcohols

β-Amino alcohols also called vicinal amino alcohols[1] are an important organic compounds containing both an amino (NH_2,NHR,NR_2) and hydroxyl (OH) functional groups which are adjacent to each other . Ethanolamine **(1)** is the simplest vicinal amino alcohol.



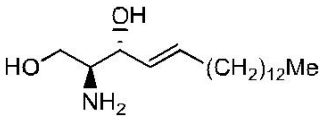
Ethanolamine **(1)**

They have been extensively used as a *β*-blockers, insecticidal agents and chiral auxiliaries.[2] The importance of *β*-amino alcohols is evident from the fact that this moiety is found in many natural products and biologically active synthetic molecules which play important role in treatment of various human diseases. This moiety is found in many biologically active alkaloid, peptides[1] and lipids. Lipids containing *β*-amino alcohol moiety includes sphingosine **(2)** which is vital regulator of many physiological and pathophysiological processes e.g. carcinoma, diabetes and osteoporosis.[3]

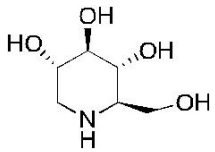
Hydroxy amino acids constitute a major group of naturally occurring compounds containing *β*-amino alcohol moiety. Cyclic amino alcohol is another class of naturally occurring vicinal amino alcohols in which amino residue is remained within the ring .This group is represented by deoxynojirimycin **(3)**,which is an alpha glycosidase inhibitor isolated from mulberry leaves and is important due to its low cytotoxicity.[4]

Quinine **(4)** isolated from cinchona tree bark is used as a drug having active potential against malarial parasite ,fever and other diseases.[5] Hapalosin **(5)** found in blue green alga *Hapalosiphon welwitschii* has a strong anticancer property.[6]

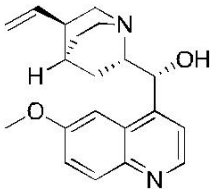
Besides their use in medicinal chemistry *β*-amino alcohols are important in synthetic organic chemistry as (+) N- methyl ephedrine **(6)** isolated from *Ephedra distachya* has found its use as chiral ligand and resolving agents.



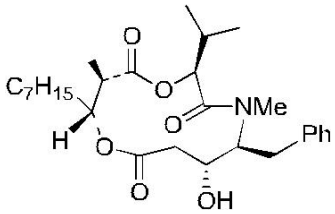
Sphingosine **(2)**



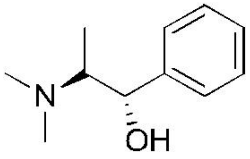
Deoxynojirimycin **(3)**



Quinine **(4)**



Hapalosin **(5)**

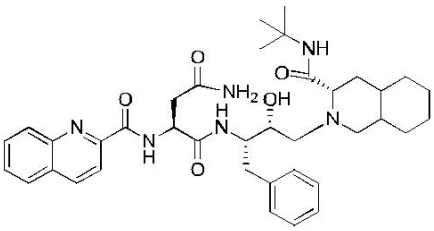


(+) N-methyl ephedrine **(6)**

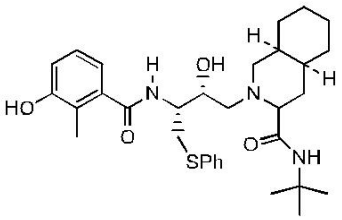
Naturally occurring *β*-amino alcohol derivatives

Peptidomimetics are the most important among synthetic biologically active *β*-amino alcohol derivatives. This group of peptide analogues is exemplified by the HIV protease inhibitor saquinavir[1] **(7)** and nelfinavir **(8)**.

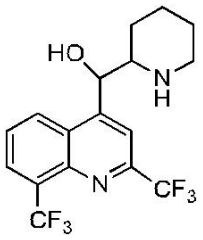
The *β*-amino alcohol moiety is also present in many other synthetic compounds like mefloquine **(9)** and Ethambutol **(10)**[7] which are clinically established anti-malarial and anti-mycobacterial drugs respectively.



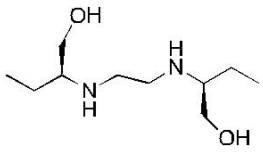
Saquinavir **(7)**



Nelfinavir **(8)**



Mefloquine **(9)**



Ethambutol **(10)**

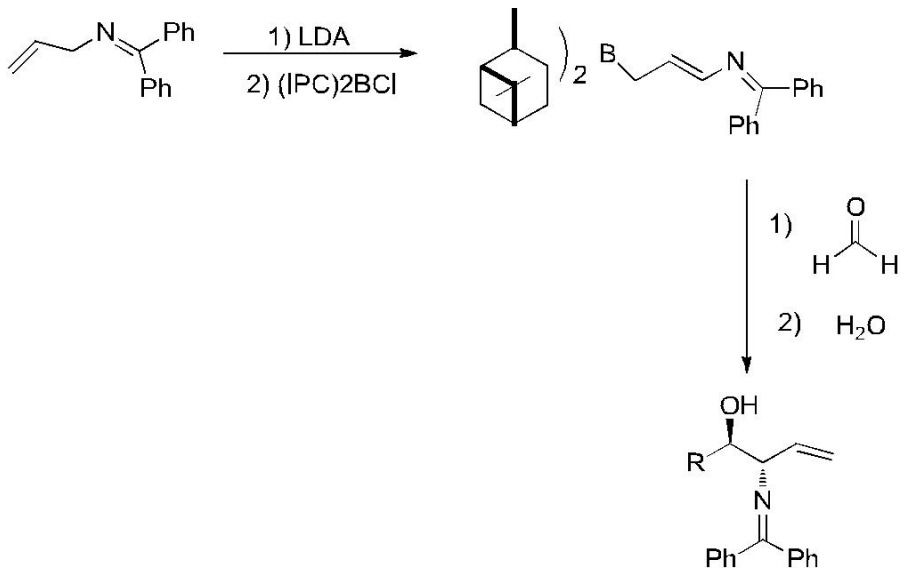
Synthetic biologically active *β*-amino alcohol derivatives

1.2 Synthesis of *β*-Amino Alcohols

Synthetic path towards enantiopure 2-amino alcohols have generally count on derivatization of chiral pool of amino acids with instinctive draw backs of attainable target.[8]To overcome those limitations considerable efforts have been made to develop asymmetric routes to vicinal amino alcohols which can be divided into two different perspectives. Most commonly the amino alcohol moiety can be insert into pre-existing carbon skeleton. Another efficient method for vicinal amino alcohol's synthesis is coupling of carbons and creations of one or two vicinal stereo genic centres in single step.

1.21 *β*-Amino Alcohols from Carbon coupling

Synthesis of *β*-amino alcohols by *α*- addition of 3-amino allyl borane to aldehyde involves first the transformation of allylic imines to 3-amino allyl borane. Vinylic 1, 2-amino alcohols with high diastereoselectivity can be achieved when chiral borane reagents are used[9] **(scheme 1)**.



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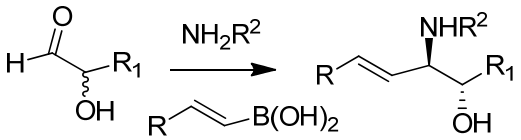
Scheme (1): Amino allyl borane addition to aldehydes

In a three components boronic acid Mannich approach Petasis reported a sophisticated synthetic strategy of *anti*-amino alcohols. Imine is formed by condensation of *α*-Hydroxy aldehyde with amine which in turn reacted with boronic acid derivatives to obtain the anti-amino alcohols with high diastereoselctivity.[10]The major drawback of this reaction is the requirement for aryl or olefinic boronic acid derivatives **(scheme 2)**. [11]



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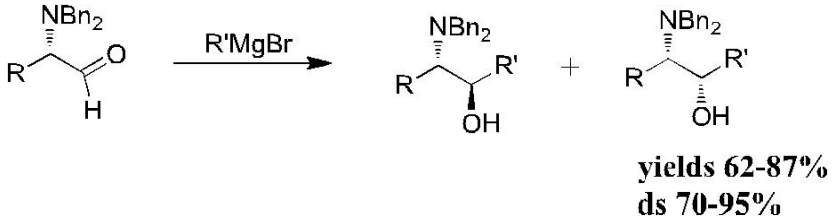
Scheme (2): Boronic Acid Mannich Reaction

Synthesis of *β*-amino alcohol by addition of organometallic nucleophiles to *α*-amino carbonyl is good method because when one of the two stereo centre is set the other can be generated with excellent diastereoselectivity. But the limitations of this method is the stability problems of ***α***-amino carbonyls and sometimes moderate diastereoselectivity is achieved **(scheme 3)**.[12]



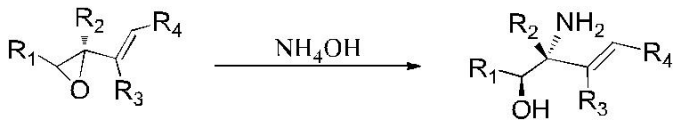
Scheme (3): Nucleophilic addition to ***α***-amino carbonyls

1.22 *β*- Amino Alcohol by Reaction without Changing Carbon Skeleton

Mostly the amino alcohols are created without changing the carbon skeleton. The substrates are particularly alkene or alkene derivatives and the reaction carry on stereo specifically. Furthermore these reactions generally lead to regioselectivity problems. Although this is a prime concern, it can be evade by using substrate substituted with region directing groups.

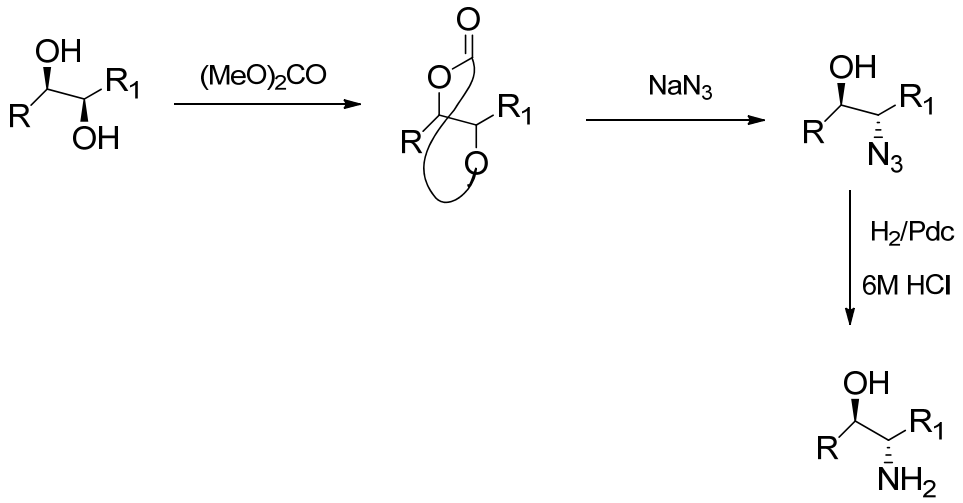
Opening of epoxide with nitrogen nucleophile is presumably the most important path towards synthesis of enantiomerically pure 2-amino alcohols. Due to high availability of enantiomerically pure (*cis* and *trans* isomer) of epoxides, this approach can be used for the synthesis of both *syn* and *anti β*-amino alcohols.

The regioselectivity of epoxide opening is usually poor but can be controlled by introducing conjugating groups e.g. phenyl or vinyl, the hard nucleophile mostly attack at the activated benzylic and allylic carbon respectively **(scheme 4).**[13, 14]



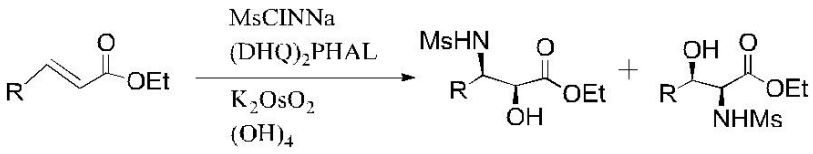
Scheme (4): Aminolysis of Vinyl Epoxides

Besides epoxide ring opening reaction, *β*-amino alcohols can also be synthesized from *syn* diols. This reported method involves the conversion of *syn* diol to cyclic carbonate which upon attacking of NaN_3 and subsequent reduction gives 2-amino alcohol **(scheme5)**.



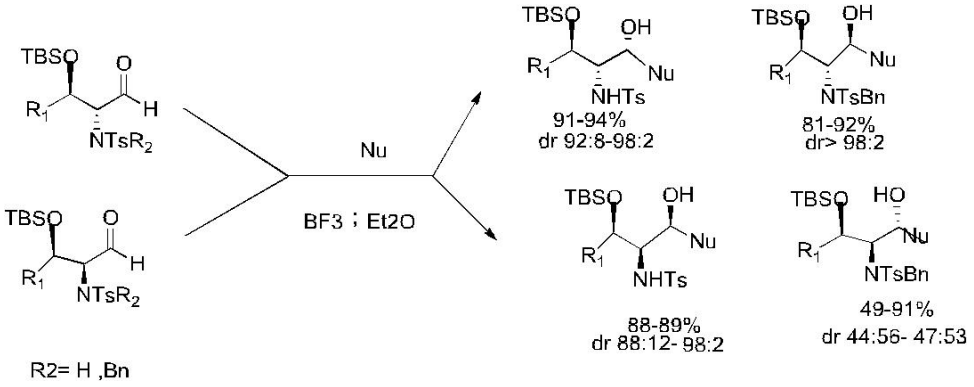
Scheme (5): Nucleophilic opening of cyclic carbonates

Preparation of enantioselective *β*-amino alcohols by sharp less asymmetric amino hydroxylation of alkene derivatives is the most direct route.[15] The chiral catalyst used in this reaction is same as that utilized in asymmetric dihydroxylation reaction.[16,17]Although this approach is interesting towards enantioselective synthesis of 2-amino alcohols but the yields are often moderate due to regioselectivity problems **(scheme 6).**



Scheme (6): Sharp less Asymmetric Amino hydroxylation

Another approach in which stereo directing effect of pre-existing stereo genic centre works is nucleophilic addition to ***α***-amino aldehydes, which usually results in good diastereoselectivity. One recent example on a disparate procedure for substrate controlled diastereoselective synthesis of amino diols based on nucleophilic Mukayama aldol addition to *α*-amino *β*-silyloxy aldehydes is given bellow[18] **(scheme 7).**



Scheme (7): Diastereoselective Mukayama Aldol Addition

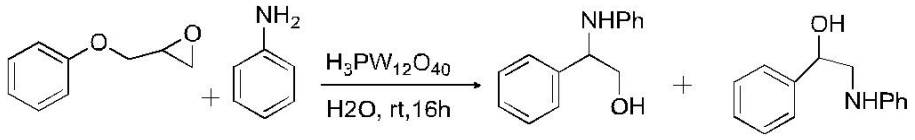
1.23 Some Earlier Synthetic Approaches of *β* – Amino Alcohols

S.V Malhorta *et al*. reported synthesis of vicinal amino alcohol via aminolysis of epoxide, reaction condition included ionic liquid 1-ethylpyridinium trifluoro acetate **(scheme 8).**[19]These reactions took place under mild conditions without any catalyst and high yields of *β*-amino alcohols were achieved. Further increase in yield and rate of reaction was observed by using $AlCl_3$ as a catalyst.

(Scheme 8)

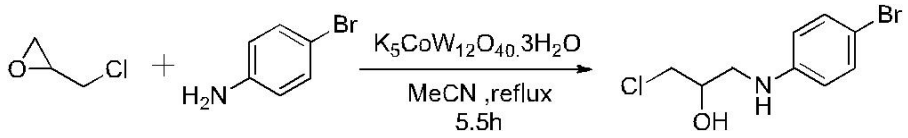
Another earlier approach for synthesis *β*-amino alcohol was by ring opening of epoxide in the presence of heteropoly acid (catalyst), which was found as best catalyst in ring opening of epoxides with different aromatic amines **(scheme 9).**[20]

This high yielding method was reported by M. R. Saidi *et al* which provides an efficient, clean and easy synthetic route for preparation of *β*-amino alcohols.



(Scheme 9)

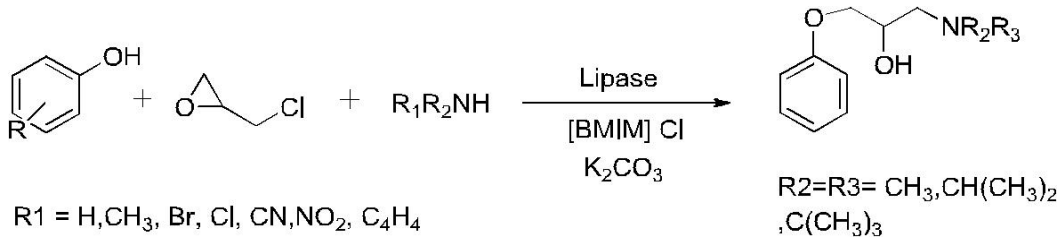
E .Rafiee *et al* reported a high selective, an efficient and more convenient method for the synthesis of 2-amino alcohols by aminolysis of epoxides in the presence of catalyst ($K_5CoW_{12}O_{40}.3H_2O$) with different amines **(scheme 10).**



(Scheme 10)

1.24 One Pot Synthesis of *β*-Amino Alcohol

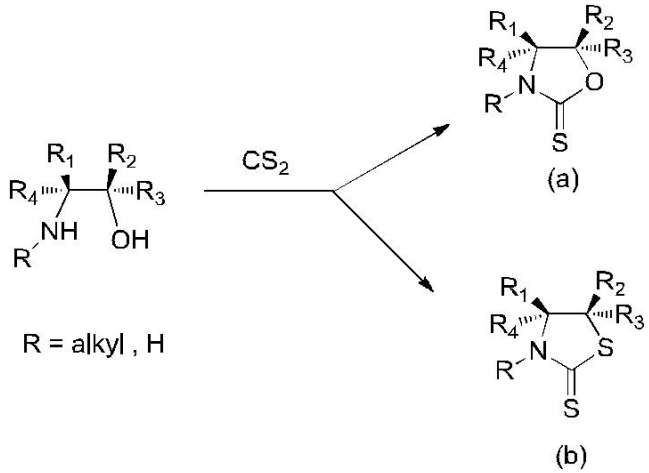
Vasant S.Borude *et al* reported a new simple one pot synthetic strategy for synthesis of *β*-amino alcohol derivatives, phenol, epychlorohydrin and amines reacted together in presence of phase transfer catalyst and lipase biocatalyst and pharmacologically active vicinal amino alcohols were obtained with excellent yield and high regioselectivity **(scheme 11).**[21]



(Scheme 11)

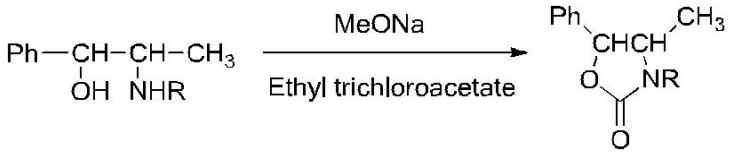
1.3 Reactivity of *β*- Amino Alcohol

β-Amino alcohol having two functionalities as amino and hydroxyl groups play important role in organic synthesis especially in synthesis of important heterocyclic compounds. As these two functional groups act as nucleophile selectively and by reaction with other organic compounds having electrophilic centre give new compounds. *β*-Amino alcohols can have alcoholic group either primary secondary or tertiary but it does not have significant effect on the rate of reaction. But nature of amino group is important in term of reactivity as primary amine react readily while reaction becomes slow with secondary amine.[22]The reactivity of vicinal amino alcohol can be understand by the following reactions.



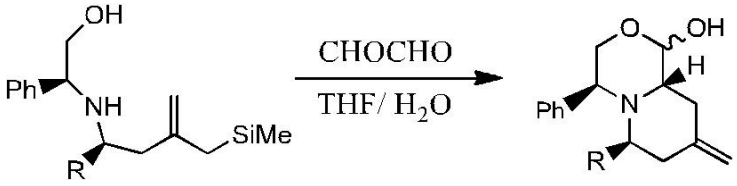
(Scheme 12)

The two functionalities react selectively as N of amino group being a more nucleophilic group attack on electrophilic centre which here is electrophilic carbon of carbon disulphide and two possible products can be obtained. In the above reaction it was reported that in strong alkaline medium the compound **(a)** was not formed while compound **(b)** was obtained selectively. Another example includes base catalysed reaction of *β*-Amino alcohols with trihaloacetate **(scheme 13).**[23]



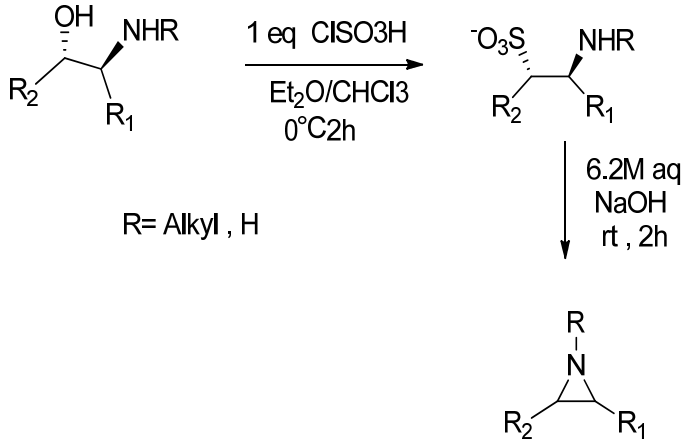
(Scheme 13)

Intramolecular cyclization is an important reaction of *β*-Amino alcohol in which the two nucleophiles react with intramolecular electrophilic centre and cyclize to form new hetrocyclic compounds **(scheme 14).**[24]



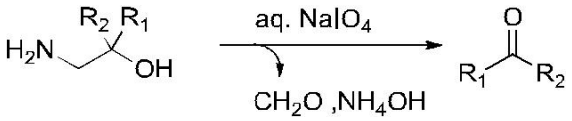
(Scheme 14)

Another important intramolecular cyclization reaction of *β*-amino alcohol is in acidic medium which leads to important heterocycles aziridine **(scheme 15)**.[25]



(Scheme 15)

The alcoholic group of vicinal amino alcohol undergoes oxidation in presence of oxidizing agent e.g. aq $NaIO_4$ and leads to their respective aldehydes and ketones **(Scheme 16)**.[26]



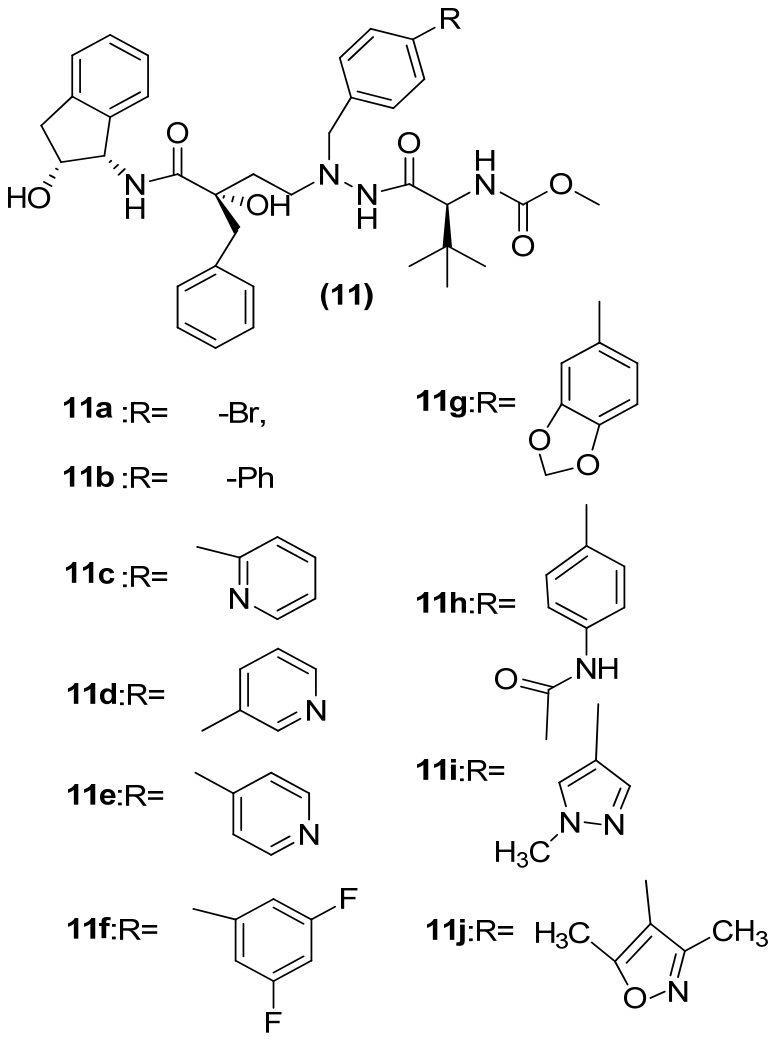
(Scheme 16)

1.31 Biological Application (Literature Review)

β-Amino alcohols are important organic compounds having two functionalities adjacent to each other and can found both naturally as well as synthetically. Vicinal amino alcohol moiety has found its importance in medicinal chemistry and organic synthesis as well. Biological importance of *β*-amino alcohols include their applications as anticancer drug, anti HIV, antimalarial, antimicrobial, antihypertensive ,anti- tuberculosis and antioxidant agents.

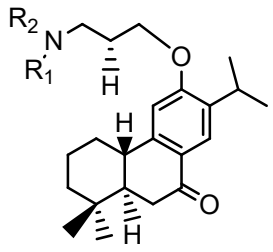
1.32 Anti-HIV Activity

Along with other drug HIV-1 drugs, the protease inhibitors provide extended life period with better quality of life by actively supressing the formation of new virus particles in patients. In 2010 Mats Larhed *et al* reported some compounds containing *β*-amino alcohol moiety which were achieved with little modification in the basic structure of the known series of HIV-1 protease inhibitor which after screening proved to be more potent **(11)**.[27]



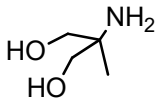
1.33 Anticancer Activity

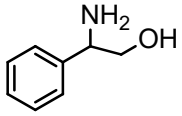
In 2006 J. M. Padron *et al* reported a series of *β*-amino alcohol derivatives of sugiol which were synthesized in a simple way. The in vitro proliferative activities of these compounds were tested in human solid tumour cell lines which showed high potential in growth inhibition in panel of three sundry human solid tumour cells. The derivatives achieved with secondary amines subunit found more active than those bearing tertiary amine moiety. On the basis of all these results it was concluded that these compound would be active against both sensitive and resistant solid tumours. In short the vicinal amino alcohol derivatives of sugiol appeared to be the most potent molecule in development of advanced anti-tumour agents.[28]



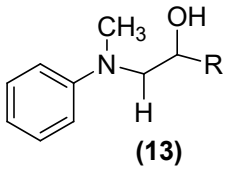
(12)

12a:Amine = n-$C_{12}H_{25}NH_2$
12b:Amine =$PhCH_2CH_2NH_2$
12c: Amine = Morpholine
12d:Amine = Adenine
1**2e**:Amine = Bn_2NH
12f:Amine =$(n\text{-}C_5H_{11})_2NH$

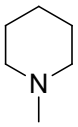
12g:Amine = 

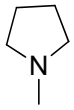
12h: Amine = 

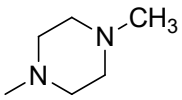
D. Sharma et al reported a series of 3-(N-alkyl - N- phenyl amino) propan-2-ol derivatives **(13)** which were synthesized in a multistep strategy and were screened for their inhibitory activity against SrC Kinase and anti-cancer activity on human breast cancer cells.[29]

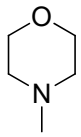


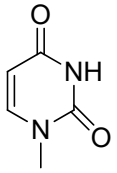
(13)

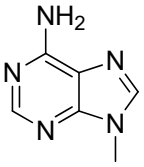
13a:R = 

13b:R = 

13c:R = 

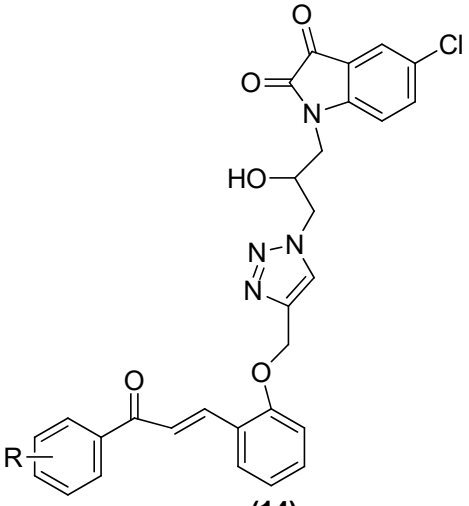
13d:R = 

13e:R = 

13f:R = 

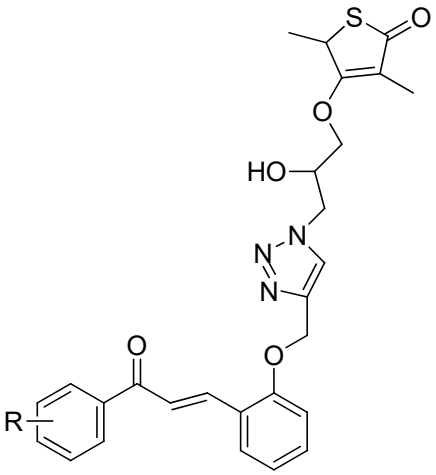
1.34 Antimalarial Activity

R. H. Hans *et al* reported the synthesis and biological screening of two new series of natural product like hybrids which were based on the chalcone, thiolactone and isatin subunits. As a result of biological screening it was shown that the *β*-amino alcohol derivatives of thiolactone chalcone were more potent against W2 stain Plasmodium falciparum then derivatives of isatin chalcone. The *β*-amino alcohol triazole with isatin chalcones subunit showed fali pain -2-inhibitory activity whereas the thiolactone chalcones were deprived of such enzyme inhibitory activity.[30]



(14)

14a:R = 4-methoxy
14b:R =2,4-dimethoxy
14c:R = 2,3,4- trimethoxy

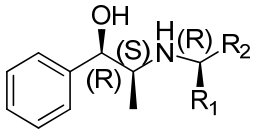


(15)

15a:R = 4-methoxy
15b:R = 2,4-dimethoxy
15c:R = 2,3,4- trimethoxy

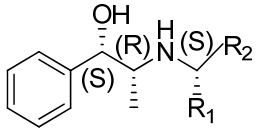
1.35 Antimicrobial Activity

Microorganism can affect the quality of water, air, food which in turn results in spreadness of diseases and infections. Antimicrobial agents are chemical substances which kills or inhibits growth of various micro-organisms e.g. bacteria, fungi, algae etc. Many vicinal amino alcohols show wide range of biological activities. Keeping in view the biological importance of *β*-amino alcohols in 2014 P.T. Perumal *et al* were synthesized N-alkylated *β*-amino alcohols with 100% enantioselectivity. The synthesized compounds were screened for antimicrobial activities via disc diffusion method as a result of this screening it was shown that **(16d), (16d')** were very active against bacteria and funji.[31]



100 % ee

16a,**16b**,**16c**,**16d**



100 % ee

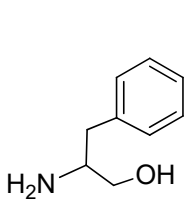
16a,**16b'**,**16c'**,**16d'**

16a:R1= methyl
16b:R1 = methyl
16c:R1 = ethyl
16d:R 1= methyl

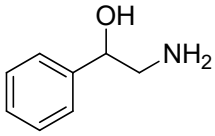
R_2=Phenyl
R2 = isobutyl
R2 =phenyl
R2 =p-methoxy phenyl

1.36 Antioxidant

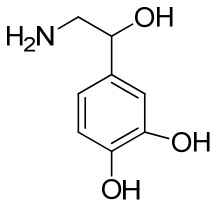
β-Amino alcohols have been broadly reported acting as chemical marker motivating self defence mechanism of plants against oxidative stress. In 2015 the electroanalytical data of some *β*-amino alcohols revealed that they possess moderate to strong antioxidant properties.[32]Some of these *β*-amino alcohol derivatives are as follows.



(17)



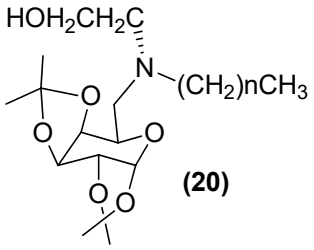
(18)



(19)

1.37 Anti tubercular Activity

In 2007 A. F. Taveria *et al* synthesized a series of *N* and *C* alkylated amino alcohol derivatives and were screened against tuberculosis virulent strain H37RV using rifampicin as reference for activity. Among these, five compounds showed good biological activity with a minimum inhibitory concentration below 12.5 μg/ml. It was noted that length of alkyl chain was also effective in the activity of these compounds e.g. *N*-dodecyl-ethanolamine and C-decyl-ethanolamine showed activity with MIC (0.027 mM) and MIC (0.015 m M) respectively. While in glycosylated derivatives the activity observed with MIC value was (0.006 mM) which was determined as the most active.[33]



(20)

CH3(CH2)nNHCH2CH2OH

(21)

[CH3(CH2)n]2NCH2CH2OH

(22)

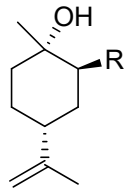
CH3(CH2)nCHCH2NH2
OH

(23)

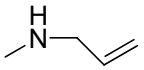
n = 5
n = 7
n = 9

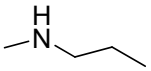
1.38 Anti leishmanial Activity

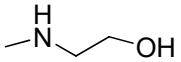
Parasitic diseases are the cause of death mostly in the under developed areas, like other parasitic diseases leishmaniasis is also parasitic disease for which multiple species of leishmania (protozoa genera) are responsible. In order to find way to prevent these diseases people busy in research and many of them became successful in their goals. Similarly in 2008 Stela R. Ferrarini *et al*[34] synthesized a series of seven limonene β-amino alcohol derivatives which upon screening found to be significantly effective against in vitro cultures of the leishmania braziliensis the activity for **(24b)** and **(24f)** were about 100 times more effective than the standard drug.

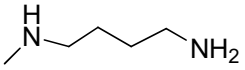


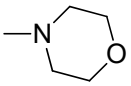
(24)

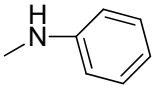
24a:R = 

24b:R = 

24c:R = 

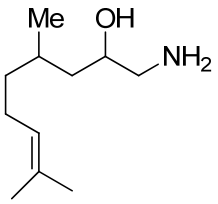
24d:R = 

24e:R = 

24f:R = 

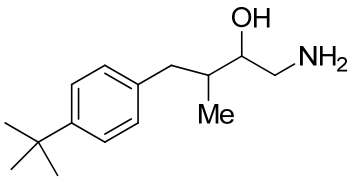
1.4 Other Applications

Besides medicinal uses *β*-amino alcohols have their applications in other fields as well e.g some simple *β*-amino alcohols are used as solvents and high boiling bases. Diethanolamine condensate an important *β*-amino alcohol derivative found its use in preparation of shampoo, conditioner, lipstick, hair dyes, soap bars, creams, and detergents. In perfumery industry vicinal amino alcohol derivatives found an important use e.g. they are used as properfumes. In 2003 Jean Louis Reymond *et al*[26] reported a novel properfume strategy, the *β*-amino alcohol properfumes are non-volatile, stable compounds releasing fragrant carbonyls (aldehydes, ketones) by oxidation with per iodate oxidant in water. *β*-Amino alcohol derivatives of citronellal **(25)**, lilial **(26)**, lauryl aldehyde **(27)**, menthone **(28)** and anisaldehyde **(29)** were some reported examples of properfumes.



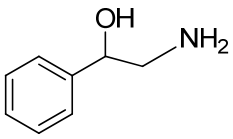
Pro-citronellal

(25)



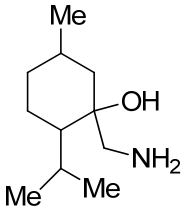
Pro-lilial

(26)



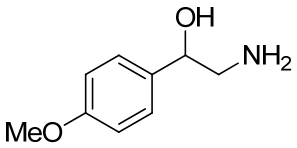
Pro-lauryl aldehyde

(27)



Pro-menthone

(28)

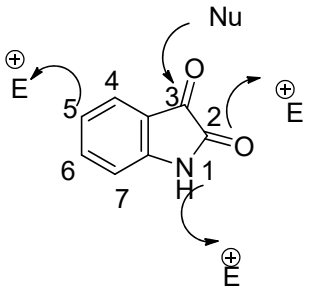


Pro-anisaldehyde

(29)

1.5 Reactivity of Isatin

Isatin first investigated by Erdman and Laurent which is 1H –indole -2,3-dione has an indole nucleus and two carbonyl groups one is keto the other is lactam. Isatin has four reactive sites two of which undergoes attack on electrophiles while the other two are an electrophilic centres. Carbonyl at position **3** is very reactive and undergoes condensation especially important in Schiff base reactions.[35]



N of isatin undergoes alkylation in two main conditions either in weak basic medium or by formation of salt of isatin. *O*-Alkylation at position **2** along with *N*-alkylation has also been reported.[36] Isatin also undergoes aromatic electrophilic aromatic substation at position **5** of aromatic ring.

1.6 Importance of Isatin moiety

Compounds containing isatin moiety have broad range of biological and pharmacological properties and are commonly used as substrate for the synthesis of many organic heterocycles and for drug as well.

Applications of isatin derivatives includes antibacterial,[37]antifungal , anti HIV,[38] anticonvulsant,[39] antitumoral, anti-inflammatory, antihelminthic and anticancer[40] properties. Drugs having isatin moiety are used to cure diseases like bulimia, epilepsy,[41] tuberculosis.[42, 43]

2.1 Plan of Work

β-Amino alcohols are the compounds of immense importance and have attracted considerable attention from organic and bio-organic chemistry community in the last few decades. Similarly, the isatin (Indole-1*H*-2,3-dione) is undoubtedly a privileged scaffold for chemical modification due to its presence in a number of naturally occurring substances and its derivatives have been reported to have diverse biological applications. Therefore, keeping the importance of these two structural moieties in view, we thought it worthwhile to have some new compounds (**Figure 2.1**) containing both of these structural moieties.

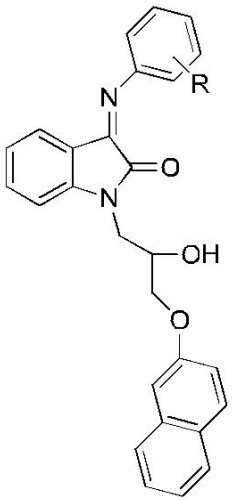


Figure 2.1: General structure of the designed *β*-amino alcohols

Thus, the current project was designed, which include,

1) the synthesis of naphthyloxy methyl oxirane.

2) the synthesis of isatin-based *β*-amino alcohols by the reaction of naphthyloxy methyl oxirane with isatin.

3) the synthesis of Schiff base derivatives of *β*-amino alcohols by taking the advantage of isatin C-3 carbonyl reactivity.

4) the exploration of medicinal applications of the synthesized compounds.

2.2 Instrumentation

Melting points of all the synthesized compounds have been determined in open capillary tubes by using Gallenkamp apparatus (MP-D) and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker spectrometer at 300 and 75 MHz respectively in CDCl3 and DMSO using residual solvent signals as a reference. Chemical shifts are given in δ (ppm) scale. Spin multiplicities are indicated by following by abbreviations, s, dd, d, m for singlet, double doublet, doublet, multiplet respectively. The GC-MS spectra were performed with Agilent 5973 inert mass selective detector in combination with Agilent 6890 N gas chromatography. The progress of reactions were monitored by thin layer chromatography by using pre-coated silica gel 60 F_{254} aluminium plates. The chromatographs were visualized under UV light (254–365 nm). The synthesized *β*-amino alcohol derivatives were purified by recrystallization using mixture of ethanol and ethyl acetate.

2.3 Substrate and Reagents

2-Naphthol, Epichlorohydrin, KOH, Isatin, Aniline, K_2CO_3, Acetic acid, 2-Chloro aniline,2- Methyl aniline, 2,4-Dimethyl aniline, 4-Methyl aniline, 2-Methoxy aniline, 3-Methoxy aniline, DMF, Ethanol, DMSO, Ethyl acetate, n-Hexane, Chloroform, DCM, $MgSO_4$ (anhydrous) and Acetone, all these chemicals were purchased from Sigma Aldrich and Merck.

2.4 Drying and Purification of solvents

All the solvents were purified and dried as given bellow before using them.

2.41 DMF

N,N- Dimethyl formamide (DMF) was purified in such a way that anhydrous calcium sulphate ($CaSO_4$) 100 g was added to 500 ml of DMF in round bottom flask and allowed to stand it overnight, filtered and distilled under reduced pressure and stored on molecular sieves (4°A).

2.42 Ethanol

Ethanol was first obtained from spirit by distillation under reduced pressure then was refluxed over calcium oxide (CaO) and by its redistillation at 77 to 78° C 99 % pure ethanol was obtained.

2.43 Methanol

Commercial methanol first distilled then was reflux over calcium oxide and pure methanol was obtained by redistillation at 64 to 65° C.

2.44 Ethyl acetate

It was purified in such a way that first it was shaken with 5% Na_2CO_3then with saturated brine solution it was then dried standing over calcium oxide (CaO) and followed by distillation at 77 °C.

2.45 Chloroform

Chloroform was dried by adding anhydrous calcium chloride and allowed to stand it for 3 hours then distilled at 64 to 65° C.

2.46 n-Hexane

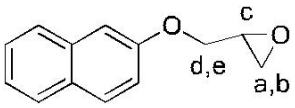
n-Hexane was purified by allowing it to stand over calcium hydride (CaH_2) for 4 hours, filtered and distilled it at 69° C.

2.5 General Procedure for Synthesis of Naphthyloxy Methyl Oxirane

49.6 mmol (2.78 g) of KOH pellets were grinded and converted to powder form. Naphthol 27 mmol (3.97 g) was taken and dissolved in 8 ml of DMSO, KOH powder was also added and stirred at room temperature for 35 minutes and was followed by drop wise addition of 82.7 mmol (7.657 g, 6.48 ml) of epichlorohydrin.[44]

The completion of reaction was monitored by TLC with regular intervals of time. After completion reaction was quenched by adding ice cold water and was extracted with chloroform 75 ml and (75×5) portions of water. Then washed three times with brine solution. The organic layer was collected and dried over anhydrous $MgSO_4$ filtered and concentrated over rotary evaporator. The light brown coloured crude product was obtained which was dissolved in hot n-hexane and white shiny pure product was achieved. Physical, NMR and GC/MS data are as follows.

(1a) Naphthyloxy Methyl Oxirane



(1a)

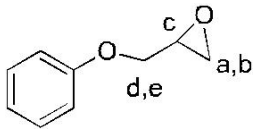
Yield 90 %; white shiny solid; m.p. 65-66 °C; Rf=0.69 (n-hexane : ethyl acetate 5:1); ^{1}H NMR (300 MHz, DMSO) δ 2.7 (1H dd, J_{ac}=2.7 Hz, J_{ab}=5.1 Hz, H_a), 2.88 (1H, dd, J_{bc}=4.2 Hz, J_{ba}=5.1 Hz, H_b), 3.415 (1H, m, H_c), 3.943 (1H, dd, J_{dc}=6.6 Hz, J_{de}=11.4 Hz, H_d), 4.456 (1H, dd, J_{ec}=2.7 Hz, J_{ed}=11.4 Hz, H_e), 7.208 (1H, dd, J=2.4 Hz, J= 9 Hz), 7.336-7.382 (2H, m), 7.438-7.492 (1H, m), 7.793 (1H, d, J=8.1 Hz), 7.843 (2H, d, J=9 Hz), ^{13}C NMR (75 MHz, DMSO), 44.30 (CH_2-O), 50.13 (CH-O), 69.50(Ar-O-CH_2), 107.32, 119.03, 124.18, 126.92, 127.17, 128.0, 129.04, 129.86, 134.64, 156.57.

2.6 General Procedure for Synthesis of Phenyloxy methyl Oxirane (1b)

16 mmol (0.896 g) of KOH pellets were grinded and converted to fine powder. Phenol 10 mmol (0.94 g) was taken in 250 ml of 2N RBF and dissolved in 4 ml of DMSO, KOH powder was also added and stirred at room temperature for 30 min and was followed by dropwise addition of 30 mmol (2.775 g, 2.35ml) of epichlorohydrin.[44] After completion of reaction ice cold water was added to the reaction mixture and was extracted with chloroform 65 ml and (65ml ×5) portions of distilled water then washed three times with brine solution. The organic layer was collected dried over anhydrous

$MgSO_4$, filtered and solvent was removed via rotary evaporator light yellow liquid was obtained. The oily layer containing mixture of desired product and impurities was adsorbed on silica gel and was purified by column chromatography using (n-hexane: ethyl acetate in 9:1) as a mobile phase.

(1b) Phenyloxy Methyl Oxirane



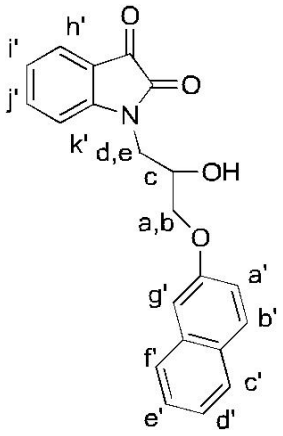
(1b)

Yield 78%; Light yellowish oily product; Rf value=0.73(n-hexane : ethylacetate 5:1); ^{1}HNMR ($CDCl_3$, 300 MHz), δ: 2.783 (1H, dd, J_{de}= 11.6 Hz, J_{dc}=7.2 Hz, H_d), 2.982 (1H, dd, J_{ed}=11.6 Hz, J_{ec}=3.2 Hz, H_e), 3.12-3.38 (1H, m, H_c), 3.984 (1H, dd, J_{ab}= 5.4 Hz , J_{ac}=3 Hz, H_a), 4.244 (1H, dd, J_{ba}=5.4 Hz, J_{bc}=4.5 Hz, H_b), 6.986 (3H, m), 7.297 (2H, m); ^{13}CNMR ($CDCl_3$, 75 MHz), δ: 44.75 (CH2-O), δ:50.18 (CH-0), 68.68 (Ar-O-CH2), 114.63 (two ortho carbon), 129.54 (meta carbon atoms), 121.24 (para carbon), 158.49 (q carbon); EIMS :m/z 150 [M+·]

2.7 General Procedure for Synthesis of 1-(2-Hydroxy-3-(naphthalen-2-yloxy) propyl) isatin (2a):

6.8 mmol (1g) of isatin and 7 mmol (1.4 g) of naphthyloxy methyl oxirane were taken and mixed in 4 ml DMF in 2 neck round bottom flask. After 15 minutes stirring at room temperature (0.093 g) of K2CO3 was added and continued to stirr at room temperature for 15 minutes then shifted to reflux. The progress of reaction was monitored by TLC after regular intervals of time. After completion reaction mixture was extracted with (75 ml × 5) water and 75 ml of ethyl acetate. The organic layer was collected and solvent removed over rotary evaporator. A crude orange solid was obtained which upon recrystallization in ethanol gave 2.0 g pure crystalline orange product.

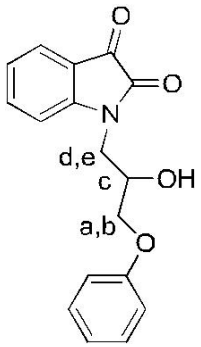
(2a) 1-(2-Hydroxy-3-(naphthalen-2-yloxy) propyl) isatin



(2a)

Yield 85%; Orange crystals; m.p.133-134°C ,Rf = 0.15 (n-hexane : ethyl acetate, 2:1) , ^{1}H NMR (300 MHz $CDCl_3$), δ 3.083 (1H, d ,OH, *J*=4.8 Hz), 4.007 (2H, d, J = 5.4 Hz, H_d ,H_e) , 4.123 (1H, dd, J_{ab} = 9.6 Hz, J_{ac}= 4.8 Hz, Ha), 4.194 (1H, dd , J_{ba}=9.6 Hz , J_{bc}= 6.3 Hz, H_b), 4.42- 4.47 (1H, m, H_c), 7.066 - 7.177 (4H , m), 7.34–7.39(1H, m), 7.433 – 7.483 (1H, m), 7.511 – 7.590 (2H , m), 7.724 (1H, d, *J*=6.6 Hz) , 7.772 (2H ,d , *J*=7.2 Hz), ^{13}C NMR (75 MHz ,$CDCl_3$), δ 43.50 (CH2-N) ,68.60 (-CHOH), 69.45 (CH2-O), 107.15, 111.08, 117.63, 118.36, 123.95, 124.05, 125.34,126.61, 126.89, 127.66, 129.25, 129.67, 134.37, 138.47, 151.29, 155.95, 159.26 (C=O , amide carbonyl), 183.01 (C=O, keto carbonyl);EIMS :m/z 347 [M+·]

(2b) 1-(2-Hydroxy-3-phenoxypropyl) indoline-2, 3-dione



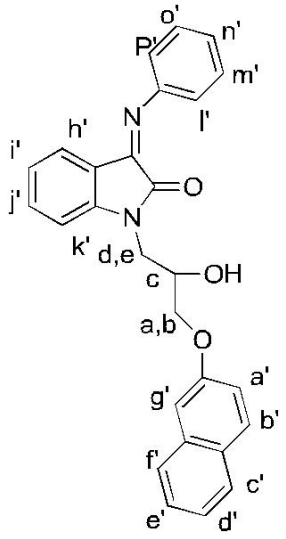
(2b)

Yield 87%; Orange crystals; m.p.152-153°C; Rf = 0.13 (n-hexane : ethyl acetate 2:1); ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.807-3.981 (2H, m, H_d, H_e), 3.995-4.058 (2H, m, H_a, H_b), 4.154-4.207 (1H, m, H_c), 5.438 (1H, d, *J*= 4.8 Hz, OH), 6.916-6.959 (3H, m), 7.117 (1H, t, *J*=7.5 Hz), 7.213- 7.330 (3H, m), 7.55 (1H, dd, *J*=7.5 Hz, *J*=2.4 Hz), 7.606-7.662 (1H, m), ^{13}C NMR ($CDCl_3$, 75 MHz), δ: 43.82 (CH2-N), δ: 66.66 (CH-O), 70.21 (Ar- O-CH2), 111.70, 114.95, 118.02, 121.11, 123.47, 124.69, 129.95, 138.43, 151.82, 158.89, 158.97 (C=O, amide carbonyl), 183.97 (C=O , keto carbonyl);EIMS :m/z 295 [M+·]

2.8 General Procedure for Synthesis of 1-(2-Hydroxy-3-(naphthalen-2-yloxy) propyl)-3-(phenylimino) indolin-2-one (3a-3h)

12 mmol (1.116 g) of aniline and 10 mmol (3.47g)of 1-(2-hydroxy-3-(naphthalen-2-yloxy) propyl) isatin **(2a)** were mixed in 15 ml of ethanol in 2N round bottom flask, 2 to 3 drops of acetic acid were added and reaction mixture was set at reflux. After precipitation of the product the reaction mixture was removed from reflux and filtered. The yellow precipitates were recrystallized from ethanol and ethyl acetate mixture and 2.678 g of pure solid product was obtained.

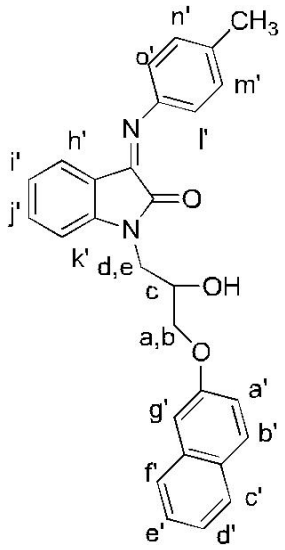
(3a) 1-(2-Hydroxy-3-(naphthalen-2-yloxy) propyl)-3-(phenylimino) indolin-2-one



(3a)

Yield 65%; Light orange solid m.p. 102-103°C; Rf = 0.14 (n-hexane : ethyl acetate, 2:1), ^{1}H NMR (300 MHz, $CDCl_3$), δ: 3.083 (1H, d, *J*=4.5 Hz, OH), 3.98 (2H, dd, $J_{de,ed}$ =5.7 Hz, $J_{dc,ec}$=3.6 Hz, H_d, H_e), 4.196 - 4.293 (2H, m, H_a, H_b), 4.493-4.529 (1H, m, H_c), 7.043 (1H, dd, *J*=7.2 Hz, *J*=1.2 Hz), 7.168-7.215 (4H, m), 7.331-7.481 (7H, m), 7.755-7.801 (4H, m), ^{13}C NMR (75 MHz, $CDCl_3$), 43.59 (CH2-N), 66.70 (CHOH), 70.23 (CH2OH), 107.21, 115.80, 117.81, 119.19, 120.30, 122.49, 123.09, 124.89, 126.22, 127.25, 128.89, 129.23, 129.87, 130.52, 134.58, 134.62, 134.71, 148.90, 149.20, 155.43, 159. 89 (C=O amide carbonyl), 163.20 (C=N).

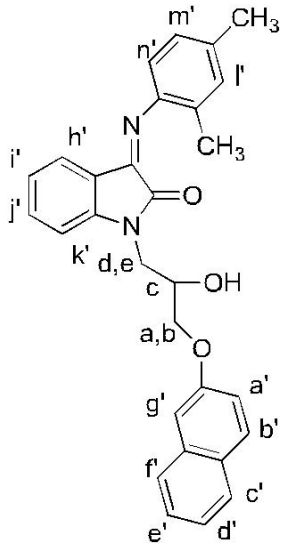
(3b) 1-(2-Hydroxy-3-(naphthalen-2-yloxy) propyl)-3-(p-tolylimino) indolin-2-one



(3b)

Yield 86%; Orange solid; m.p .143-145°C; Rf = 0.10 (n-hexane : ethyl acetate , 2:1); ^{1}H NMR (300 MHz , DMSO), δ 2.365 (3H, s, CH_3), 3.924-3.948 (2H, m, H_e, H_d), 4.089 -4.284 (3H, m, H_a, H_b, H_c), 5.513 (1H, d, *J*=4.8 Hz OH), 7.096 -7.487 (11H, m), 7.789 -7.851 (4H, m), ^{13}C NMR (75 MHz, DMSO), δ: 21.06 (CH_3), 43.89 (CH_2-N), 66.73 (CHOH), 70.60 (CH_2OH), 107.24, 115.80, 117.82, 119.17, 120.30, 122.47, 124.09, 125.29, 126.88, 127.15, 127.98, 128.99, 129.19, 129.77, 130.54, 134.50, 134.68, 148.22, 148.35, 154.49, 159.79 (C=O, amide carbonyl), 163.10 (C=N).

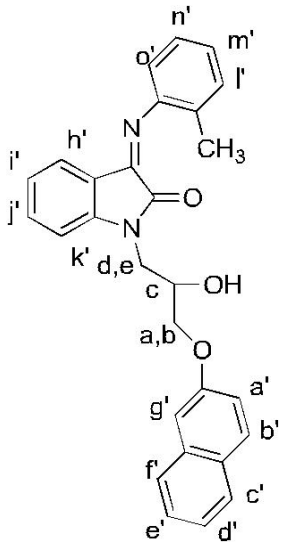
(3c) 3-((2, 4-Dimethylphenyl) imino)-1-(2-hydroxy-3-(naphthalen-2-yloxy) propyl) indolin-2-one



(3c)

Yield 85%; Reddish crystals; m.p. 116-118°C; Rf = 0.12 (n-hexane : ethyl acetat , 2:1), ^{1}H NMR (300 MHz, DMSO), δ 2.09 (3H, s, CH_3), 2.321 (3H, s, CH_3), 3.805-3.842 (2H, m, H_d, H_e), 3.966-4.315 (3H, m, H_a, H_b, H_c), 5.573 (1H, d, *J*=5.4 Hz, OH), 6.702-6.810 (2H, m), 6.429 (1H, d, *J*=7.5 Hz), 6.999-7.221 (4H, m), 7.275-7.483 (4H, m), 7.791-7.849 (3H, m), ^{13}C NMR (75 MHz, DMSO), 21.06 (CH_3), 21.20 (CH_3), 43.99 (CH_2-N), 66.72 (CHOH), 70.64 (CH_2OH), 107.24, 111.25, 116.12, 116.72, 119.17, 122.68, 124.10, 124.97, 125.80, 126.88, 127.16, 127.85, 127.99, 129.00, 129.78, 131.90, 131.92, 134.55, 134.69, 147.05, 148.19, 154.58, 156.79 (C=O, amide carbonyl), 163.02 (C=N).

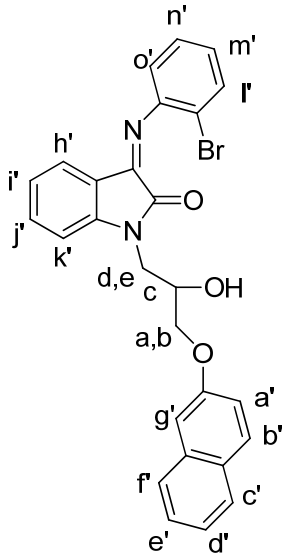
(3d) 1-(2-Hydroxy-3-(naphthalen-2-yloxy) propyl)-3-(o-tolylimino) indolin-2-one



(3d)

Yield 62%; yellow solid; m.p. 95-97°C; Rf = 0.17 (n- hexane : ethyl acetate, 2 : 1), ^{1}H NMR (300 MHz, $CDCl_3$), δ 2.28 (3H, s, CH_3), 3.352 (1H, b s, OH) 3.682 (1H, dd, J_{ed} =7.6 Hz, J_{ec}=2.2 Hz, H_e), 3.801 (1H, dd, J_{da}=7.6 Hz, J_{dc}= 2.5 Hz, H_d), 4.190-4.302 (2H, m, H_a, H_b), 4.222-4.922 (1H, m, H_c), 6.990 (1H, dd, *J*=8.1 Hz, *J*=8.9 Hz), 7.221-7.562 (11H, m), 7.890-7.971 (3H, m), ^{13}C NMR (75 MHz ,$CDCl_3$), δ 21.09 (CH_3), 43.82 (CH_2-N), 66.35 (CHOH), 70.50 (CH_2OH), 107.81, 115.92, 117.30, 118.52, 118.90, 124.20, 125. 98, 126.90, 127.50, 127.86, 127.98, 128.33, 128.60, 129.32, 129.40, 129.48, 129.88, 130.11, 131.44, 144.11, 147.62, 154.49, 158.22 (C=O, amide carbonyl), 163.22 (C=N).

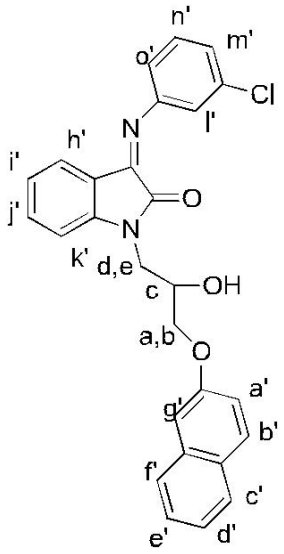
(3e) 3-((2-Bromophenyl) imino)-1-(2-hydroxy-3-(naphthalen-2-yloxy) propyl) indolin-2-one



(3e)

Yield 72%; Yellowish solid; m.p. 119-120°C; Rf = 0.17 (n-hexane : ethyl acetate, 2: 1); ^{1}H NMR (300 MHz, DMSO), δ 3.79(1H, dd, J_{ed}=9 Hz, J_{ec}=2.1 Hz), 3.94 (1H, dd, J_{de} =9 Hz, J_{dc}=2.3 Hz), 4.18-4.29 (2H, m, H_a, H_b), 4.42-4.90 (1H , m, H_c), 5.052 (1H, d, J=4.8 Hz, OH), 7.12-7.48 (7H, m), 7.49-7.58 (3H, m), 7.83-7.90 (5H, m), ^{13}C NMR (75 MHz, DMSO), 43.70 (CH_2-N), 66.79 (CHOH), 70.64 (CH_2OH), 107.40, 115.6 3, 117.80, 118.12, 118.90, 124.30, 126.60, 126.92, 127.53, 127.71, 127.92, 128.10, 128.71, 129.31, 129.40, 129.52, 129.60, 130.80, 131.11, 143.62, 147.82, 155.30, 159.20 (C=O, amide carbonyl), 163.83 (C=N).

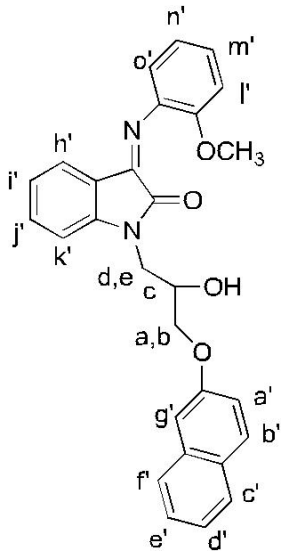
(3f) 3-((3-Chlorophenyl) imino)-1-(2-hydroxy-3-(naphthalen-2-yloxy) propyl) indolin-2-one



(3f)

Yield 70%; Brownish yellow crystals; m.p.112-114°C; Rf = 0.10 (n-hexane : ethyl acetate, 2:1); ^{1}H NMR (300 MHz, DMSO), 3.795-3.954 (2H, m, H_d, H_e), 4.094-4.282 (3H, m, H_a, H_b, H_c), 5.538 (1H, bs, OH), 6.395 (2H, d, *J*=7.5 Hz), 7.048-7.473 (10H, m), 7.769-7.854 (3H, m), ^{13}C NMR (75 MHz, DMSO)**,** δ 43.90 (CH_2-N), 66.60 (CHOH), 70.56 (CH_2OH), 107.24, 111.49, 115.64, 116.49, 117.50, 118.97, 119.16, 123.21, 124.10, 125.54, 127.16, 127.99, 128.98, 129.98, 130.50, 131.98, 134.67, 134.81, 134.99, 147.54, 148.63, 151.12, 156.72 (C=O, amide carbonyl), 162.88 (C=N).

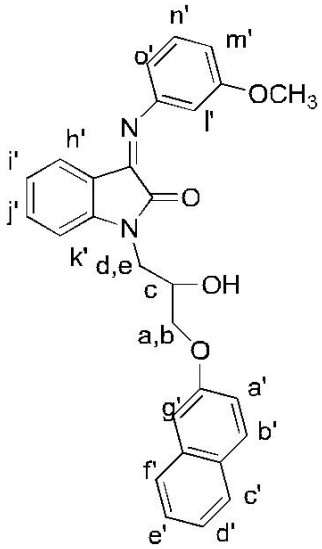
(3g) 1-(2-Hydroxy-3-(naphthalen-2-yloxy) propyl)-3-((2-methoxyphenyl) imino) indolin-2-one



(3g)

Yield 67%; Orange solid; m.p. 109-111°C; Rf = 0.08 (n-hexane : ethyl acetate, 2: 1), ^{1}H NMR (300 MHz, $CDCl_3$), δ 3.354 (1H, bs, OH), 3.802 (3H, s, OCH_3), 3.572 (1H, dd, J_{de}=7.4 Hz, J_{dc}=2.3 Hz, H_d), 3.733 (1H, dd, J_{ed}=7.4 Hz, J_{ec}=2.6 Hz, H_e), 4.191 - 4.320 (2H, m, H_a, H_b), 4.395-4.490 (1H, m, H_c), 6.690 – 7.231 (4H, m), 7.262 – 7.392 (3H, m), 7.480-7.523 (3H, m), 7.872- 7.953 (5H, m), ^{13}C NMR (75 MHz, $CDCl_3$), 44.89 (CH_2-N), 55.22 (OCH_3), 65.89 (CH-OH), 70.82 (CH_2OH), 107.24, 115.32, 115.80,115.91, 117.30, 118.30, 122.40, 124.10, 124.50, 124.80, 126.20, 126.85, 127.52, 128.90, 129.50, 129.60, 129.80, 131.10, 139.40, 146.92, 152.20, 155.60, 158.82 (C=O, amide carbonyl) , 163.20 (C=N).

(3h) 1-(2-Hydroxy-3-(naphthalen-2-yloxy) propyl)-3-((3-methoxyphenyl) imino) indolin-2-one

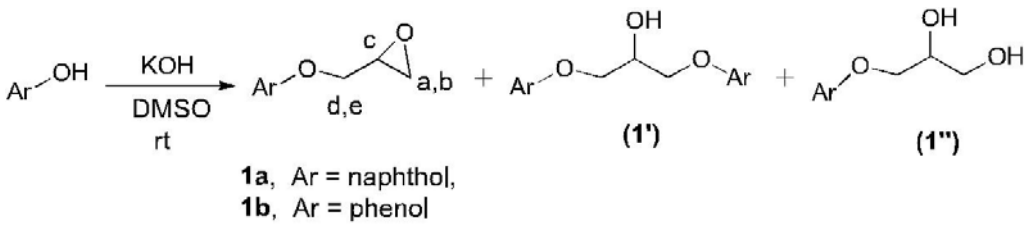


(3h)

Yield 67%; Brownish solid; m.p.102-104°C; Rf=0.08 (n-hexane : ethyl acetate, 2 :1), ^{1}H NMR (300 MHz**,** $CDCl_3$), δ: 3.820 (3H, s, OCH_3), 3.354 (1H, bs, OH), 3.542 (1H, dd, J_{de}=7.6 Hz, J_{dc}=2.4 Hz), 3.722 (1H, dd, J_{ed}=7.6 Hz, J_{ec}=2.3 Hz), 4.190-4.321 (2H, m, H_a, H_b), 4.480-4.521 (1H, m, H_c), 6.561–6.990 (3H, m), 7.191-7.262(3H, m), 7.391-7.592 (4H, m), 7.841-7.972 (5H, m), ^{13}C NMR (75 MHz, $CDCl_3$), 44.86 (CH2-N), 55.26, (OCH_3), 65.89 (CHOH), 70.53 (CH_2OH), 107.20, 115.22, 115.82, 115.98, 117.32, 118.32, 122.40, 124.10, 124.50, 124.82, 126.22, 126.85, 127.52, 128.90, 129.52, 129.60, 129.80, 131.20, 139.42, 146.90, 152.20, 155.62 , 158.80 (C=O, amide carbonyl), 163.30 (C=N).

3.1 Synthesis of 1-(2-Hydroxy-3-(naphthalen-2-yloxy) propyl)-3-(phenyl imino) indolin-2-one (3a-3h)

The preparation of Schiff base derivatives of *β*-amino alcohols were initiated by synthesis of naphthyloxy methyl oxirane by *O*–alkylation of naphthol with epichlorohydrin in presence of strong base KOH and DMSO as a solvent at room temperature. It was observed that at room temperature the yield was excellent because at room temperature the formation of side products isolated as compound (**1'** and **1''**) was only in traces but at high temperature e.g. up to 60 °C the yield of desired product became low due to formation of more side products. The proposed mechanism of the reaction expected to involve the naphthoxide ion formation first which would attack on the less hindered side of the epoxide ring and leads to the opening of epoxide ring .In the presence of strong base the in situ ring closure would lead to the product formation (**1a** and **1b**).



Scheme 3.1

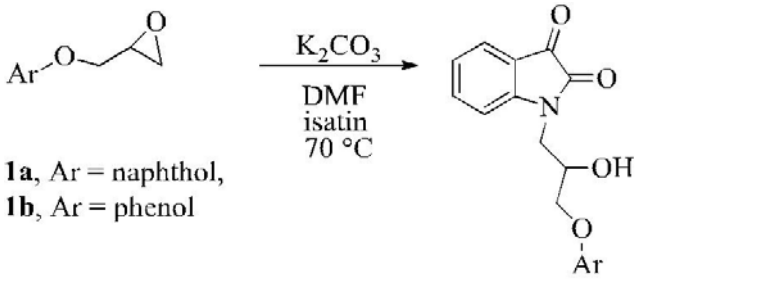
The synthesized compounds **1a** and **1b** were identified and confirmed by comparing their melting points and proton NMR and ^{13}C NMR and GC/MS spectroscopic data with those of the literature. As the proton NMR data showed four diastereotopic protons for compound (**1a**) as H_a at 2.7 as dd with coupling constant 2.7 and 5.1 Hz and H_b observed at 2.8 ppm as dd with J = 4.2 and 5.1 Hz while H_d gave signal at 3.95 as dd with coupling constants of 6.6 and 11.4 Hz the other diastereotopic proton appeared at 4.456 as dd with J= 2.7 and 11.4 Hz. The ^1H NMR spectrum of compound (**1b**) showed H_a at 3.98 and H_b at 4.24 both as dd while H_d and H_e observed at 2.78 and 3.95 respectively. In both compound **1a** and **1b** the H_c of the chiral carbon appeared as multiplet at 3.49 and 3.98 respectively. The absence of OH signal in ^1H NMR and appearance of seven proton in aromatic region for **1a** and five for **1b** were important conformational points. The physical data e.g. melting points, physical states, Rf values and % yields were given in table **3.1.**

Table 3.1 Physical data of compound (1a and 1b)

Compound No	Ar	Physical state	M.P (°C)	Rf	Yield %
1a	Naphthol	White shiny solid	65 -66	0.69	90
1b	Phenol	Oily liquid		0.73	78

(n-hexane: ethyl acetate, 5:1)

Naphthyloxy methyl oxirane (**1a** and **1b**) were then treated with (isatin which is biologically important compound) in presence of DMF (solvent) and weak base potassium carbonate at 70° C for 8 and 6 hours to get new compound **2a** and **2b** respectively in good yields **(Scheme 3.2).**



1a, Ar = naphthol,
1b, Ar = phenol

2a , Ar = naphthol
2b , Ar = phenol

Scheme 3.2

The reaction was tried under different conditions which are given below in table **(3.2).**

Table (3.2) Optimizations of Reaction Conditions

Solvent	Base (K_2CO_3)	Temperature (°C)	Time (h)	Yield %
2-Propanol	0.3 eq	Rt	24	No reaction
	Catalytic amount	50	16	No reaction
	0.4 eq	80	10	15
	Catalytic amount	80	12	25
2-Butanol	Catalytic amount	85	16	10
	0.4 eq	80	14	Traces
DMF	0.4 eq	50	14	40
	Catalytic amount	70	8	85
	0.3eq	70	7	65
	Catalytic amount	50	18	50

Reaction was not took place from room temperature to 50°C in secondary alcohol (2-propanol). In the same solvent the reaction took place at 80°C and rate of reaction increased with increase in amount of base potassium carbonate, as it was noted that the yield was 25% when using catalytic amount of base and 15% when using 0.4 eq of base. It was observed that the mild base K_2CO_3 acted as acid scavenger and when used in catalytic amount gave slight better yield in comparison with base used as 0.3 eq or more.

In 2-Butanol by using catalytic amount of base 10% yield was obtained but by increasing the amount of base the increase in rate of reaction was observed but yield became very low as only traces of product were observed which might be due to low polarity of solvent. Aprotic polar solvent DMF proved as a best solvent as at 70°C by using catalytic amount of potassium carbonate 85% yield was obtained and under the same reaction condition by only increasing the amount of base the yield decreased as 65% and one of the side product more polar then desired product and soluble in water, was formed more whenever the amount of K_2CO_3 increased.

The synthesized compounds (**2a**) and (**2b**) were confirmed on the basis of spectral data of GC/MS, ^{1}H NMR, ^{13}C NMR. Physical states, melting points and Rf values are given in table (**3.3**).

Table (3.3) physical data of (2a and 2b)

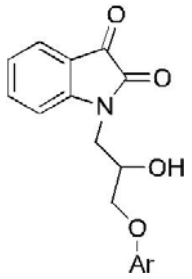
Compound No	Ar	Physical state	M.P (°C)	Rf (value)	Yield%
2a	Naphthol	Orange crystals	133-134	0.15	85
2b	Phenol	Orange crystals	152-153	0.13	87

(n-hexane : ethyl acetate , 2:1) for **2a**

(n-hexane : ethyl acetate , 2:1) for **2b**

The ^{1}H NMR of compound **2a** presented the two methylene protons (H_e and H_d) connected to the carbon next to nitrogen at 4.00 as a doublet with coupling constant 5.4 Hz by coupling with H_c. From proton NMR the structures were confirmed by appearance of -OH signal at 3.083 ppm as doublet with coupling constant 4.8 Hz for (**2a**) and at 3.25 ppm as broad singlet for (**2b)**, H_c appeared in the range 4.42 -4.47 as multiplet for (**2a**) while observed as multiplet in the range of 3.66–3.90 for (**2b**). The two diastereotopic methylene protons H_a and H_b of (**2a**) appeared at 4.12 and 4.19 as a double doublet with coupling constant 9.6 Hz and 4.8 Hz and for H_a and 9.6 Hz and

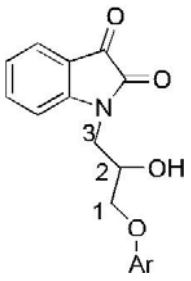
6.3 Hz for H_b, for **2b** these two protons observed at 3.92 and 4.22 ppm as dd. The structures of the compound **2a** and **2b** were further confirmed from its ^{13}C NMR spectra in which the characteristic peak for C=O (keto carbonyl) appeared at 183.10 ppm and C=O (amide carbonyl) appeared at 159.26 ppm for (**2a**) and for (**2b**) C=O appeared at 183.97 ppm and amide C=O observed at 158.97 ppm.GC/MS spectra had shown the molecular ion peak of (**2a**) at m/z =347 and the same peak for (**2b**) observed at m/z =295.



Fgure (3.1)

Table (3.4) the ^1H NMR data of 2a and 2b

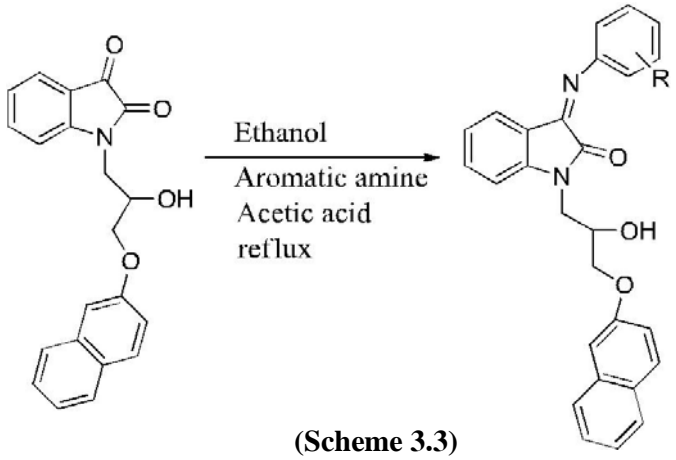
Compound No	Ar	δ, integration, multiplicities, coupling constants
2a	Naphthol	3.083 (1H, d, J =4.8 Hz ,OH), 4.123 (1H, dd, J_{ab} = 9.6 Hz, J_{ac}= 4.8 Hz, H_a), 4.194 (1H , dd J_{ba} = 9.6 Hz, J_{bc} = 6.3 Hz, H_b) ,4.007 (2H, d, J_{ed} =J_{de}= 5.4 Hz, H_e, H_d), 4.420- 4.470 (11H, m, H_c)
2b	Phenol	5.438 (1H, d, J=4.8 Hz, OH), 3.962-4.058 (2H, m, H_a, H_b), 3.807-3.981 (2H, m, H_d, H_e), 4.154-4.207 (1H, m, H_c),



The ^{13}C NMR data of compound (2a and 2b) given is table (3.5)

Compound No	Ar	δ (ppm)
2a	Naphthol	C_1 (43.50), C_2 (68.60), C_3 (69.45),C=O (keto) (183.10), (C=Oamide)159.26
2b	Phenol	C_1 (43.82), C_2 (66.66), C_3 (70.21),C=O (keto) (183.97), C=Oamide,(158.9)

The compound **(2a)** was then reacted with aromatic amine in pure ethanol in presence of few drops of acetic acid at reflux and Schiff base product was obtained **(scheme 3.3).**



(Scheme 3.3)

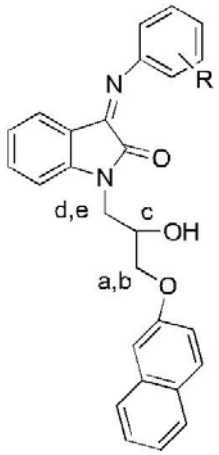
The formation of the new compounds (**3a -3h**) were indicated by their melting points and R_F values and were confirmed from ^1H and ^{13}C NMR data as the disappearance of peak around 183 ppm which is characteristic peak of (C=O keto carbonyl) and appearance of new peak around 162 to 163 ppm (C=N) confirmed the synthesis of the compounds (**3a–3h**).

Table (3.6) physical data of the (3a-3h)

Compound No	R	Physical state	M.P (°C)	Rf	Yield%
3a	H	Light orange solid	102-103	0.14	65
3b	4-CH_3	Orange solid	143-145	0.10	86
3c	2,4-dimethyl	Reddish crystals	116-118	0.12	85
3d	2-CH_3	Yellow solid	95-97	0.17	72

Compound No	R	Physical state	M.P (°C)	Rf	Yield %
3e	2-Br	Yellow solid	138 - 140	0.17	72
3f	3-Cl	Brownish yellow crystals	112 - 114	0.10	70
3g	2- OCH_3	Orange solid	109 - 111	0.08	67
3h	3-OCH_3	Brownish solid	102 - 104	0.08	67

(n-hexane :ethyl acetate,2:1)



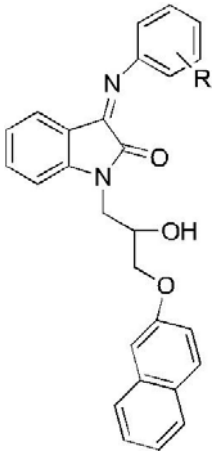
(3)

Table 3.7 ^{1}H NMR data of series (3a – 3h)

Compound No	**R**	**Chemical shift (ppm), integration, multiplicity, coupling constants(*J*=Hz)**
3a	H	3.08, 1H, d, 4.5Hz, OH; 3.98, 2H, dd, J_{de}= J_{ed}=5.7Hz, J_{dc}= J_{ec}=3.6Hz; 4.196-4.293, 2H, m, H_a, H_b; 4.493-4.529, 1H, m, H_c
3b	4-CH3	2.365, 3H, s, CH_3; 5.513, 1H, d, *J*= 4.8Hz, OH; 3.924-3.948, 2H, m, H_d, H_e; 4.089-4.284, 3H, m, H_a, H_b, H_c
3c	2,4-dimethyl	2.090, 3H,s,CH_3; 2.321, 3H, s, CH_3; 3.805-3.842, 2H, m, H_d, H_e; 3.966-4.315, 3H, m,H_a,H_b, H_c; 5.573, 1H, d, *J*=5.4Hz

3d	2-CH_3	2.280, 3H, s, CH_3; 3.35, 1H, bs, OH; 3.682, 1H, dd, J_{ed}=7.6Hz, J_{ec}=2.2Hz, H_e; 3.801,1H, dd, J_{de}=7.6Hz, J_{dc}=2.5Hz, H_d; 4.190-4.302, 2H, m, H_a, H_b; 4.222-4.922, 1H, m, H_c
3e	2-Br	5.052, 1H, d, J=4.8Hz, OH; 3.79, 1H, dd, J_{ed}=9Hz, J_{ec}=2.1Hz, H_e; 3.94, 1H, dd, J_{de}= 9 Hz, J_{dc}= 2.3Hz, 4.18 – 4.29, 2H, m, H_a, H_b; 4.42 -4.90, 1H, m, H_c
3f	3-Cl	5.538, 1H, bs, OH; 3.795-3.954, 2H, m, H_d, H_e; 4.094-4.282, 3H, m, H_a, H_b, H_c
3g	2-OCH_3	3.354, 1H, bs, OH; 3.807, 3H, s, OCH_3, 3.572,1H, dd, J_{de}=7.4Hz, J_{dc}= 2.3Hz, H_d; 3.733,1H, dd, J_{ed} =7.4 Hz, J_{ec}= 2.6Hz, H_e; 4.191-4.320, 2H,m, H_a, H_b; 4.395 – 4.490, 1H, m, H_c
3h	3- OCH_3	3.354, 1H, bs, OH; 3.820, 3H, s, OCH_3; 3.542,1H, dd, J_{de}=7.6Hz, J_{dc}=2.4Hz, H_d; 3.72, 1H, dd, J_{ed}=7.6Hz, J_{ec}= 2.3Hz, H_e; 4.190-4.321, 2H, m, H_a, H_b; 4.480-4.521, 1H,m, H_c

The ^{13}C NMR data of the series **(3a -3h)** was given in the table (**3.8)**



(3)

Table (3.8) ^{13}C NMR data of series (3a-3h)

Compound No	R	δ(ppm)
3a	H	C=O, 159.89; C=N, 163.20
3b	4-CH_3	C=O , 159.79; C=N, 163.10; CH_3, 21.06
3c	2,4-dimethyl	C=O, 156.79; C=N, 163.02;CH3, 21.06; CH3, 21.20
3d	2-CH_3	C=O, 160.22; C=N, 163.22; CH3,21.09
3e	2-Br	C=O, 159.20; C=N, 163.83
3f	3-Cl	C=O,156.72; C=N,162.88
3g	2-OCH_3	C=O, 158.82; C=N, 163.20; OCH_3, 55.27
3h	3-OCH_3	C=O, 158.80; C=N , 163.30; OCH_3, 55.26

Conclusion

A series of new isatin-based *β*- amino alcohol derivatives (3a-3h) have been synthesized in three steps. The first step involves the synthesis of naphthyloxy methyl oxirane by the reaction of 2-naphthol with epichlorohydrin, which was then further treated with isatin in the second step to obtained isatin-based *β*-amino alcohol. Taking the advantage of C-3 carbonyl reactivity, this isatin-based *β*-amino alcohol was then reacted with different aromatic amines in the third step to afford targeted Schiff base derivatives of *β*-amino alcohol (3a-3h). All the synthesized compounds were obtained in good to excellent yields (65% -86%). The structures of all the synthesized compounds were established on the basis of by their nuclear magnetic resonance (NMR) and mass spectral (GC-MS) data. Due to the presence of two biologically important structural moieties i-e isatin and *β*-amino alcohol, the synthesized compounds can be expected to have good medicinal properties. However their biological screening is still in progress.

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