Sudan University of Science and Technology

College of Graduate Studies

Synthesis of some β- amino acetophenone derivatives

تخليق بعض مشتقات بيتا أمينو اسيتوفينون

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(B. Sc. Chem. lab. Sc.)

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بسم الله الر حمن الر حيم

قال تعالى:

(قل إنما أنا بشر مثلكم يوحى إلي أنما إلهكم إله واحد فمن كان يرجوا لقاء ربه فليعمل عملا صالحا ولا يشرك بعبادة ربه احدا)

صدق الله العظيم

سورة الكهف الاية (110)

Dedication

To

My parents

For making everything worthwhile

My brothers and sister

For giving me love and inspiration

My friends

For their abundant support and their love

Acknowledgements

Acknowledgement firstly and finally to Allah who gave me the will to accomplish this work.

Then, I am grateful to all who generously contributed their time and efforts to help me to complete this project accurately and as useful as possible. Specially my supervisor Prof. Dr. Ahmed Elsadig for his guidance, care, great support and encouragement throughout the course of this work.

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List of abbreviations

C	Celcius
g	gram
g/L	gram/liter
h	hour
IR	infrared spectroscopy
Lit	literature
log*P*	logarithmic octanol-water partition coefficient
mL	milliliter
mmol	millimole
mp	melting point
NMR	nuclear magnetic resonance
o	ortho
p	para
ppm	parts per million
Rf	retention factor
α	alpha
β	beta

Abstract

The introductory chapter of this thesis outlines multicomponent reactions and describes in detail the chemistry of the Mannich reaction. The final section of the introduction deals with chemical informatics

Ten compounds of β-aminoacetophenone derivatives were synthesized by the condensation of ketone (acetophenone or *p*-bromoacetophenone) with different aromatic amines and benzaldehyde; general preparative method, ACD/lab programmer method and Swiss target prediction method for synthesized compounds were also described.

The results and discussion focused on application of ACD/Lab programmer in calculation and correlation of structure properties of the some *β*-amino acetophenone derivatives, elucidation of the structures of the synthesis compounds by various spectroscopic methods (IR and ^{1}HNMR) calculations of the percentage, Rf value and the melting point of the synthesized compounds.

الخلاصة

مقدمة هذا البحث تتحدث باختصار عن التفاعلات عديدة المركبات و توصف بالتفصيل كيمياء تفاعل مانيخ.الجزء الاخير من المقدمة يتحدث عن المعلوماتية الكيميائية.

عشرة مركبات من مشتقات البيتا امينو اسيتوفينون تم تحضيرها بتكثيف الكيتون(الاسيتوفينون او البارا بروموأسيتوفينون) مع امينات ارومانية مختلفة و البنزيالدهيد; الطريقة العامة لتخليق و طريقة برنامج ACD/lab للمركبات المخلقة تم وصفها.

النتائج و المناقشة ركزت علي تطبيق برنامج الACD/Lab في حساب الخصائص التركيبية وايجاد العلاقة بينها لبعض مشتقات بيتا امينو اسيتوفينون و توضيح تركيب المركبات المخلقة عن طريق الطرق المطيافية (الاشعة تحت الحمراء و الرنين النووي المغنطيسي). وحساب النسبة المئوية و درجات الانصهار للمركبات الناتجة.

Chapter one
Introduction

1.1. Introduction

Chemistry as a central science is facing a steadily increasing demand for new chemical entities (NCE). Innovative solutions, in all kinds of disciplines that depend on chemistry, require new molecules with specific properties. However, NCE not only demand a realistic structural space but also their feasibility poses challenges to synthetic chemists. Nowadays the question of how to perform a synthesis has become most crucial (Muller, 2011).

The synthesis of natural molecules, pharmaceuticals and other nitrogenous biologically active compounds has long been a significant branch of organic synthesis (Biller *et al.*, 2002). *β*-amino carbonyl compounds are biologically active difunctional molecules finding diverse applications in the field of medicine, besides being useful synthons for the synthesis of heterocycles, natural products, *β*-amino alcohols, amino acids, diamines and lactams (Joshi *et al*., *2010*). Syntheses of *β*-amino carbonyl compounds in an efficient and environmentally benign method have been an attractive area of research. They are, in general, prepared by:

1. Aza-Michael addition over *α*, *β*-unsaturated carbonyl compounds.
2. Multicomponent Mannich reaction.

The ideal synthesis should be simultaneously simple, safe, short, selective, high yielding, environmentally benign and based on readily available starting

materials. Additionally, the criterion of selectivity has to be matched with increasing significant economical and ecological aspects. In particular multicomponent reactions (MCR) are masterpieces of synthetic efficiency and reaction design (Azizi *et al.*, 2009 and Muller, 2011).

1.2. Multi-component reactions

Multicomponent reactions (MCRs) have been known for over 150 years. The first documented multicomponent reaction was the Strecker synthesis of α-amino cyanides in 1850 from which α-amino acids could be derived. MCRs are chemical reactions where three or more compounds react to form a single product. By definition, multicomponent reactions are those reactions whereby more than two reactants combine in a sequential manner to give highly selective products that retain majority of the atoms of the starting material. This reaction tool allows compounds to be synthesized in a few steps and usually in a one-pot operation (Armstrong *et al.*, 1996). This reaction follows by a simple purification, because all of the reagents are incorporated into the final product.

Multi-component reaction minimizes cost in the form of time and material by generating complex targets in a single convergent step (Bienayme, 2000).

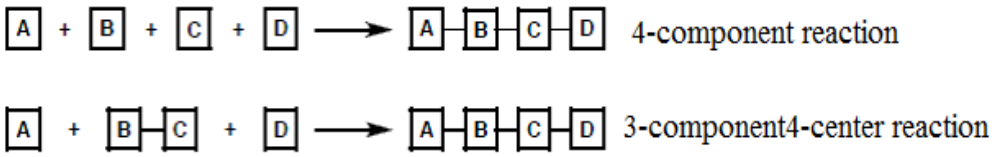
MCRs typically run at mild temperatures and do not require many reagents in excess of the participating substrates. This has made them ideal for

combinatorial library synthesis as well as industrial pharmaceutical synthesis. (Prakt, 1997; Bienayme, 2000 and Domling *et al.*, 2003)

1.3. Classification of multicomponent reactions (MCRs)

Multicomponent reactions may be classified by the number of molecules and the number of functional groups participating in the reaction (Prakt, 1997 and Bienayme, 2000).

Example:



Multicomponent reactions are also classified by the reversibility of steps leading to the product (Domling *et al.*, 2003).

Type I Substrates ⟷ [intermediates] ⟷ product

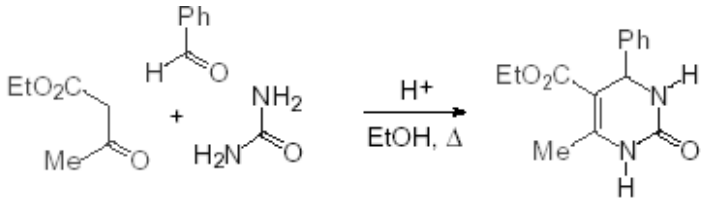
Type II Substrates ⟷ [intermediates] ⟶ product

Type III Substrates ⟶ [intermediates] ⟶ product

1.3.1. Biginelli Reaction

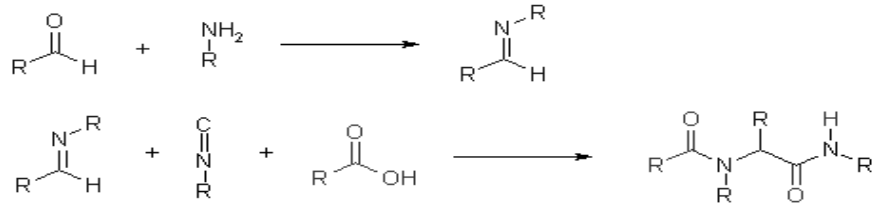
Binginelli reaction is three-component synthesis of substituted dihydropyrimidinones (Type II mechanism), first reported in 1893, and it has an increased interest because the final products have close structural relationship to the clinically important dihydropyrimidines. These compounds are known to show biological activities such as antiviral, antitumor, antibacterial, anti-

inflammatory and more recently antihypertensive agent (Piqani and Zhang 2000 and Kappe, 2000). The Biginelli reaction can be presented by the following equation:



1.3.2. **Ugi reaction** (*Type II MCR)*

The Ugi reaction is an isonitrile-based MCR that provides a rapid route for the preparation of α-aminoacyl amide derivatives. The Ugi four component condensation of an amine, oxo compound, carboxylic acid and an isocyanide is the most documented and versatile MCR(Irie *et al.*, 2011). The Ugi reaction can be presented by the following equation:



1.3.3. **Mannich reaction** (Type I MCR)

The Mannich reaction is one of the most important carbon–carbon bond forming reactions in organic synthesis for the preparation of secondary and tertiary amine derivatives (Mannich bases), (Cordova, 2004; Ishitani and Kobayashi, 1999; Prakash and Raja, 2011) which are very useful in

pharmaceutical and other biologically related areas of chemistry. (Joshi *et al.*, 2010; Azizi *et al.*, 2009; Deep *et al.*, 2012 and Subramaniapillai, 2013)

The Mannich reaction is an organic reaction which consists of an amino alkylation of substrate (R-H) possessing at least one active hydrogen with formaldehyde or other aldehyde and ammonia or a primary or secondary amine (usually as the hydrochloride). (Tramontini, 1973; Wilely, 1942; Subramaniapillai, 2013 and Chidambaranathan *et al.*, 2010)

Hence, the resulting product (the Mannich base) is an amine compound having the N atom linked to the R substrate through a methylene group. The substrate may belong to a number of different classes of compounds which includes ketones, aldehydes, acids, esters, phenols, acetylenes, picolines, nitroalkanes and quinolines (Angiolini and Tramontini, 1994).

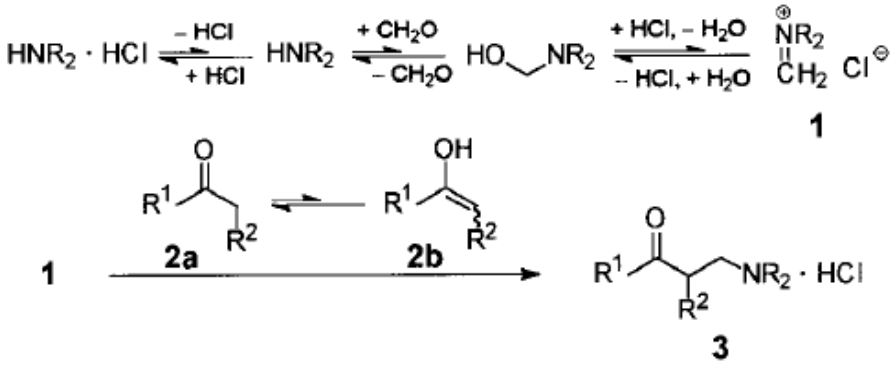
The amino alkylation of CH-acidic compounds was described by several authors as early as the 19th. Century. However, it was Carl Mannich who was the first to recognize the enormous significance of this reaction type, and it was he who extended the chemistry into a broad based synthetic methodology through systematic research. Since then this reaction that now carries his name has developed into one of the most important C-C bond-forming reactions in organic chemistry (Arend *et al.*, 1998).

The great interest in chemistry of mannich bases has been essentially inspired by two facts (Tramontini, 1973):

- The mannich synthesis introduces a basic function which can, e.g., make the molecule soluble in aqueous solvents.
- Mannich bases are very reactive; in fact, they can easily be transformed into numerous other compounds.

1.3.3.1. Synthesis of the mannich bases

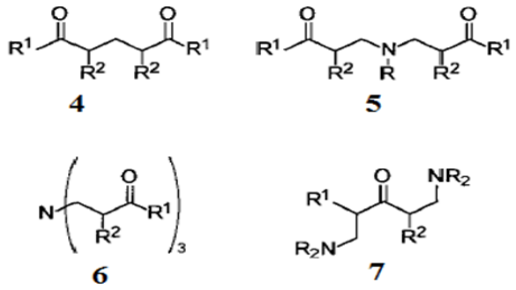
In practice, enolizable aldehydes or ketones serve as the CH-acidic substrate for Mannich reactions. In the most important variation, the carbonyl compound is heated with formaldehyde and an amine hydrochloride in a protic solvent. A simplified mechanism is given below:



It is assumed that methylene iminium salts 1 are formed in tiny amounts, by a series of equilibrium reactions. These then react with the enol tautomer 2b of the carbonyl compound 2a, also present in very small equilibrium

concentrations, to give the hydrochloride of the *β*-aminocarbonyl compound 3 (Angiolini and Tramontini, 1994).

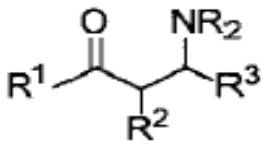
The classical Mannich reaction is, however, limited by number of serious disadvantages: due to the drastic reaction conditions and the long reaction times, unwanted side reactions often take place.



Major problems here are deamination and the formation of methylene bisketone 4. Single products 3 are generally only obtained when secondary amines are used. If one uses a primary amine or ammonia as the amine component, reaction can continue until all the H atoms on the nitrogen are replaced. One obtains in addition to the desired product 3, the other Mannich bases 5 and 6 as major components. Ketones with two reactive *α*-positions must be used in large excess, in order to avoid the production of bis-Mannich bases 7 (Angiolini and Tramontini, 1994).

In the case of unsymmetrical ketones a further problem is encountered. The regioselectivity cannot be controlled to any significant extent and is often strongly dependent on reaction conditions. Additionally, and with very few

exceptions, one can only use formaldehyde. Therefore, Mannich bases such as 8, which would very probably also be extremely attractive intermediates, are not accessible by this method.



8

A further limitation is that only aldehydes and ketones can normally be used, and other carbonyl compounds such as carboxylic acids and their derivatives cannot be aminomethylated. In addition, the classical Mannich reaction is not suited to the enantioselective synthesis of *β*-amino ketones and amino aldehydes (Hamamura *et al.*,1988).

The serious limitations of the classical Mannich reaction on the one hand, and the importance of *β*-aminocarbonyl compounds on the other has led to the search for significantly simpler synthetic methodologies. Modern versions of the Mannich reaction include synthesis of *β*-aminocarbonyl compounds through the use of preformed Mannich reagents: In comparison to the classical Mannich conditions, these preformed reagents have a higher concentration of the electrophile, leading to lower reaction temperatures and much shorter reaction times. As a consequence, many undesired side reactions, which so often cause

problems in the Mannich reaction, are avoided, even with sensitive substrates. Furthermore, one can avoid the use of protic solvents. In this way the carbonyl component can be replaced with much more reactive synthetic equivalents such as enolates. This leads to a greatly extended spectrum of application for the reaction. One can therefore also successfully use reagents which are normally impossible under the classical conditions (e.g. sterically very demanding substrates or carboxylic acid derivatives). In addition, the reaction is not restricted to aminomethylation, but aminoalkylation is also possible. It is also possible to carry out the reaction with high degrees of regio- and stereoselectivity, the most important Mannich reagents are imines, aminals and N,O acetals, iminium salts, enolates, boron enol ethers, sily enol ethers and alkyl enol ethers (Angiolini and Tramontini, 1994; Arend *et al.*, 1998; Overmann and Ricca, 1991).

Vinylogous versions of the Mannich reaction (γ-aminoalkylation of α,β-unsaturated carbonyl compounds or their derivatives) have rarely been reported. The enormous potential of this method is only now beginning to be employed synthetically (Arend *et al.*, 1998).

The asymmetric Mannich reaction is one of the most powerful carbon–carbon bond forming reactions for the construction of nitrogen-containing compounds. The utilization of this reaction allows for the preparation of

optically enriched *β*-amino carbonyl compounds and their derivatives (Cordova, 2004; Kobayashi *et al.*, 1999; Arend *et al.*, 1998; Arrayas *et al.*, 2009 and Pellissier, 2007); traditionally asymmetric Mannich reactions are catalyzed by chiral transition-metal complexes, in 2002, Biller and others described firstly the L-proline catalysed Mannich reaction. Other types of organocatalysts have also been successfully used for Mannich-type reactions (Dai *et al.*, 2007; Kano *et al.*, 2009; Jacobsen and Wenzel, 2002; Jacobsen and Yoon, 2005; Fuchibe *et al.*, 2004; Akiyama *et al.*, 2007 and Chen *et al.*, 2008).

1.3.3.2. Isolation of product of Mannich reaction

In a number of cases the salt of the desired product precipitates when the reaction mixture is cooled. Ether may be added to facilitate separation of the product. Occasionally the solvent is removed and crystallization of the residue brought about by washing it with ether or acetone. Sometimes it is advantageous to liberate the basic product from its salt and purify the former by distillation provided that the material can be distilled without decomposition (Wilely, 1942)

1.3.3.3. Reaction of Mannich bases

The main types of reactions of Mannich bases are as follows: (Tramontini, 1973)

1. Deaminomethylation involving cleavage of the R-CH_2 bond.

2. Deamination involving cleavage of the CH_2-N bond.
3. Substitution of amino group, involving cleavage of CH_2-N bond and formation of new bond, e.g. CH_2-C or CH_2-S.
4. Reduction, affecting only the group derived from the original substrate, the amino group being probably involved in the reaction.
5. Reaction with organometallic compounds.
6. Cyclization, which deals with ring closure to aminomethyl group, either at the C-atom (with elimination of the amine residue), at the N-atom, or at a substituent of the amino group.

1.3.3.4. Applications of mannich bases

The Mannich reaction and its variants are often employed to access diverse molecules, whose applications are ranging from bioactive skeletons to material science:

1. Mannich bases represent easily obtainable intermediates for synthesis of other compounds. Such as heterocycles, amino-alcohols, peptides and lactams and as precursors to synthesize amino acids (Lalitha *et al.*, 2013)
2. Mannich bases have been investigated as dyes for synthetic fibers, as reactive dyes, and also as surface active compounds. (Lalitha *et al.*, 2013)
3. Applications of Mannich reaction in bioactive molecule synthesis:

The aminocarbonyl Mannich products are useful in the construction of *β*-peptides and *β*-lactams, which are present in several bioactive molecules such as taxol (antitumour agent), bestatine (immunological response modifier) and SCH48461 (anti-cholesterol agent) (Carreira *et al.*, 2005; Roers and Verdine, 2001).

The solubility of the Mannich derivatives increases in water due to protonation of basic amine nitrogen atom (Aboel-Fadl *et al.,* 2006). Mulundocandin, a class of lipopeptides, showed excellent activity against *Candida* species. However, poor solubility restricts its widespread application, The Mannich derivatives of mulundocandin exhibited significant improvement in solubility, while retaining the activity.

Mannich reaction was useful for the preparation of zolpidem, a hypnotic drug used for the treatment of insomnia (Reddy *et al.*,2009).

The quinoline derived Mannich bases possess vasorelaxing properties. Such molecules are useful in the treatment of hypertension. (Antonucci *et al.,* 2002)

1,2,4-Triazole derived Mannich bases exhibited anticancer activity. (Holla *et al.,* 2003)

Quinoline based di-Mannich bases (Barlin *et al.,* 1997) artemisinin Mannich derivatives (Brun *et al.,* 2010) and the phenolic Mannich bases (Chibale *et al*., 2007) possess good antimalarial activity.

The anthracycline synthetic analogue 4,11-dihydroxynaphtho[2,3-f]indole-5,10-dione Mannich base (Bobrysheva *et al.*, 2005; Kearney *et al.*,1996) The gatifloxacin Mannich derivative (Kavya *et al.*, 2005) Acetophenone Mannich derivatives(Erciyas *et al.*, 2000) and chalcone Mannich bases(Bastow *et al.*,2008) showed good anticancer activity.

The Mannich reaction has been useful in the preparation of various antimicrobial molecules (Almajan *et al.,* 2009; Ashok *et al.,* 2007; Joshi *et al.,* 2005 and Kapadnis *et al.,* 2004) the presence of Mannich side chain in unsaturated Mannich ketones (Kispal *et al.*, 2001) and triazolinothione Mannich bases (Kosikowska *et al.*, 2011) increase the antibacterial activity.

Quinazoline thione Mannich bases, carboxamide derived Mannich bases and acetophenone derived Mannich bases possess good antimicrobial activity (Nayeem *et al.*, 2010; Joshi *et al.,* 2007).

Ibuprofen Mannich derivative (Kalluraya *et al.,* 2009), chalcone Mannich derivatives (Chiou *et al.,* 2011) and tetrahydroquinoline derivative (Alvaro *et al.,* 2007) showed good antiinflammatory activity.

The isothiazolopyridine derived Mannich bases were found to be 2 to 10 times more potent than the reference drug acetylsalicylic acid (Filipek *et al.*, 2005)

Mannich reaction also plays a significant role in bioactive skeleton target synthesis (Bagrjanskaja *et al.*, 2003 and Bur and Martin, 1999).

Proline catalysed asymmetric Mannich reaction played a vital role in the synthesis of *N*-terminal amino acid equivalent moiety of peptide antibiotic, nikkomycin (Hayashi *et al.*,2005).

1.4. Chemical informatics

Chemical informatics is the application of computer technology to chemistry in all of its manifestations much of the current use of cheminformatics techniques is in the drug industry, but chemical informatics is now being applied to problems across the full range of chemistry. Chemical informaticians often work with massive amounts of data. They construct information systems that help chemists make sense of the data, attempting to predict the properties of chemical substances from a sample of data, much as Mendeleev did many years ago when he accurately predicted the existence and properties of unknown elements in the periodic table. Thus, through the application of information technology, chemical informatics helps chemists organize and analyze known scientific data and extract new information from that data to assist in the development of novel compounds, materials, processes, and molecule property calculation (Ritchie, 2007).

Chemo informatics placed on four traditional research areas (Chen, 2006):

1. Chemical database systems.
2. Computer-assisted structure elucidation systems.
3. Computer-assisted synthesis design systems.
4. 3D structure builders.

1.5. Swiss target prediction

Bioactive small molecules, such as drugs, bind to proteins or other macromolecular targets to modulate their activity, which in turn results in the observed phenotypic effects. For this reason, mapping the targets of bioactive small molecules is a key step toward unraveling the molecular mechanisms underlying their bioactivity and predicting potential side effects or cross reactivity. Recently, large datasets of protein small molecule interactions have become available, providing a unique source of information for the development of knowledge-based approaches to computationally identify new targets for uncharacterized molecules or secondary targets for known molecules. Swiss target prediction is accessible free of charge and without login requirement at http://www.swisstargetprediction.ch (Daina, 2014).

1.6. ACD/Lab programmer

ACD/Lab programmer use to draw chemical structures including organics, organometallics and polymers. It also includes calculation of molecular properties (e.g., molecular weight, density, molar refractivity etc.), 2D and 3D

structure cleaning and viewing, functionality for naming structures, and prediction of log *P*.

Polarizability

Polarizability is the relative tendency of a charge distribution, like the electron cloud of an atom or molecule, to be distorted from its normal shape by an external electric field. External field can be due to presence of a nearby ion or solvent. So this effect is very important in understanding the solvent properties and reactivity of some compounds which may change when changing the solvent. polarizability increases as volume occupied by electrons increases, larger polarizability higher reactivity (Christensen *et al.*, 2002 and Anslyn, 2006).

Log*P*

The octanol-water partition coefficient, P, is a measure of the differential solubility of a neutral substance between these immiscible liquids and thereby, a descriptor of hydrophobicity (or the lipophilicity) of a neutral substance. It is typically used in its logarithmic form, log*P* (Caillard *et al.*, 1997 and Elkins *et al.*, 1971).

1.7. Aim and objectives

The Mannich reaction is an important carbon–carbon bond forming reaction in organic synthesis for the preparation of β-amino carbonyl compounds which are vital intermediates in pharmaceuticals and natural products. Attempts have been made in the past to improve methodologies based on two-component reactions, where the imine as electrophile is pre-formed and then reacted with nucleophiles such as enolates, enol ethers, and enamines. However, in most cases these protocols use hazardous organic solvents and suffer from long reaction time with low yields and poor selectivity. Therefore, the development of modern versions of the reaction that work under mild conditions is of great importance. A more appropriate version of Mannich reaction involved the one-pot three-component approach that allowed a wide range of structural variations in the reactants aldehydes, amine and ketones to give Mannich product using an appropriate catalyst.

The present work aimed at:

- Correlation the structure properties of the some *β*-amino acetophenone derivatives by ACD lab programmer.
- Synthesis of some *β*-amino acetophenone derivatives by means of an exchange reaction between the substrate (ketone) and an amine through three components one-pot Mannich reaction.

- Characterization of synthesized compounds.
- Swiss target prediction.

Chapter two
Materials and methods

2. Materials and methods

2.1. Materials

2.1.1. Solvents

Chloroform (119.38, 1.48g/L, 99.5% ROMIL LTD).

Ethanol (46.0, 99.7% , Sd fine-chem, India).

Methanol (32.04, (0.790-0.793)g/L, ADWIC ELNASR.

2.1.2. Chemicals

Acetophenone (120.15, (1.025-1.027)g/L, 99%, Benzaldehyde (106.12, (1.044-1.043)g/L, 99%, p-bromo acetophenone (199.06, 98%) Calcium chloride (110.99) Loba chemie, India.

Aniline (93.13, (1.02-1.025)g/L, 99%, Oxford laboratory, India).

p-amino benzoic acid (137.14, 99%), *p*-ancidine (123.15246), *p*-bromo aniline (199.06), Sulfanilamide (172.20), TECHNO PHARMCHEM, India).

All chemicals were used without further purification.

2.2. Thin- layer chromatography

All reactions and purity of β-amino carbonyl compounds were monitored by thin-layer chromatography (TLC) using glass plate coated with silica gel (350 mesh, 95%) obtained from sd fine-chem limited- Mumbai using 95% chloroform and 5% methanol as an eluent and the spots were visualized by iodine vapors/ultraviolet light as visualizing agents.

2.3. Infra-red spectroscopy

IR spectra (ν, cm^{-1}) were recorded on FTIR spectrophotometer obtained from SHIMADZU in KBr pellets.

2.4. ^{1}H NMR spectroscopy

^{1}H NMR spectra were recorded using DMSO as internal standard and chemical shift are in ppm.

2.5. General equipment

Melting points of the synthesized compounds were determined in open-glass capillaries on melting point apparatus. The reactions were carried out at 80 $^{\circ}$C with mechanical stirring using magnetic stirrer with hot plate obtained from Germany.

All of the glasses used were of pyrex type.

2.6. ACD lab programmer

ACD/lab free ware 2012 from www.acdlabs.com

2.7. General method of ACD/lab programmer

There were two modes to ACD/ChemSketch, namely Structure and Draw. Structure mode was used to draw chemical molecules, while Draw mode used to create and edit graphical objects. Upon startup, the Draw Normal mode and Carbon were automatically selected. By clicking and dragging the cursor in the window, C-C bonds were created. Clicking on a carbon atom produces a

branched structure. The change was made by selecting a heteroatom from the element list in the left toolbar and clicking on an atom in the structure to replace it. Radicals were made by selecting it from table which including carbon rings, carbon-based side chains and functional groups. A reaction requires were drawing by using the reaction arrow and reaction plus icons. Bond lengths and bond angle standardized by clicking on Clean Structure. The calculated properties were inserted into the ChemSketch window as a text field; on the tools menu, point to calculate, and choose the desired property (table No.3.1). By selecting a structure and clicking on generate Name for structure, the IUPAC name was generated as a text field underneath the structure (Table No.2.1), the value of the octanol-water partition coefficient (log P) also calculated (table No.3.1).

2.8. Synthetic methods

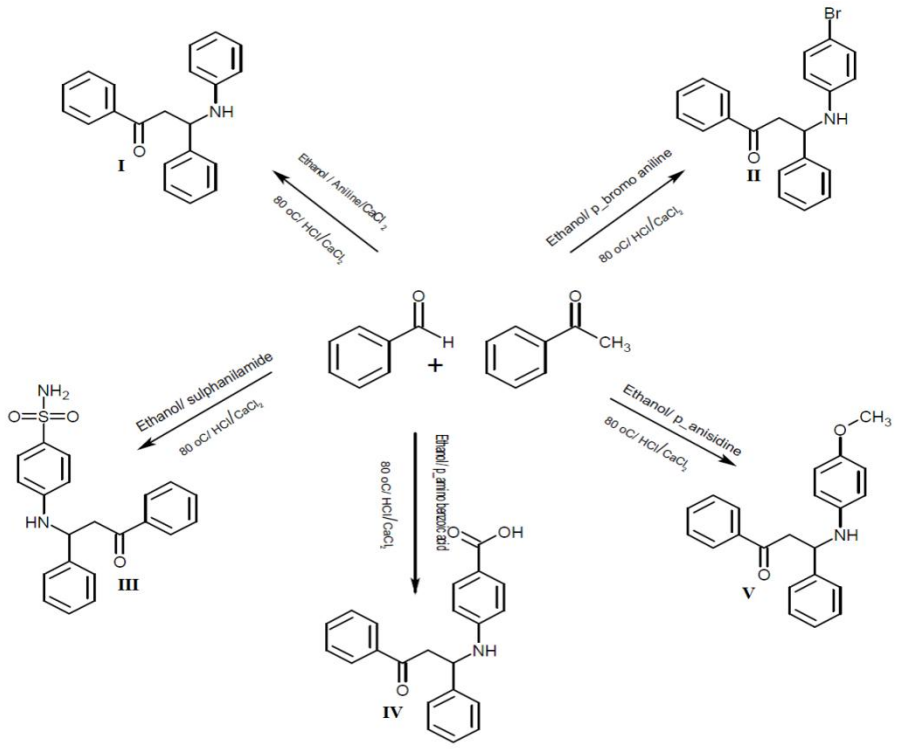
2.8.1. General method for the synthesis of β-amino acetophenone (I-V)

Mannich bases of acetophenone derivatives were synthesized as shown by the reaction schemes (2.1) one equivalent of calcium chloride was added to a mixture of acetophenone (5 mmole), benzaldehyde (5 mmole) and amine (5 mmole) in 5 ml absolute ethanol. One drop of hydrochloric acid was added. The resulting mixture was stirred at 80 ^{o}C for 2 h. the product was filtered, washed with water, and recrystallized from ethanol.

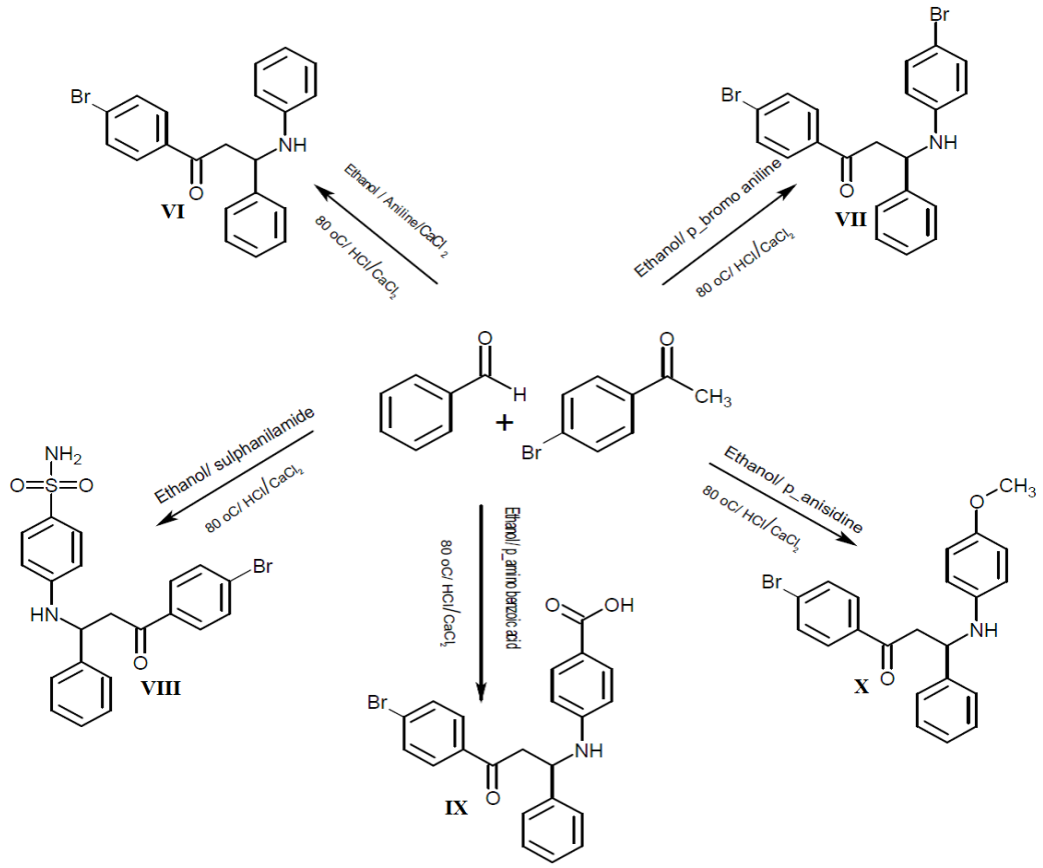
2.8.2. General method for the synthesis of β-amino *p*- bromo acetophenone (VI-X)

Mannich bases of *p*- bromo acetophenone derivatives were synthesized as shown by the reaction schemes 2.2 one equivalent of calcium chloride was added to a mixture of *p*- bromo acetophenone (5 mmole), benzaldehyde (5 mmole) and amine (5 mmole) in 5 ml absolute ethanol. One drop of hydrochloric acid was added. The resulting mixture was stirred at 80 °C for 2 h. the product was filtered, washed with water, and recrystallized from ethanol.

2.9. Reaction schemes



Scheme 2.1. Synthesis of β-amino acetophenone derivatives



Scheme 2.2. Synthesis of β-amino *p*-bromoacetophenone derivatives

2.10. Swiss target prediction method

Query molecules inputted by drawn in 2D using the javascript-based molecular editor of ChemAxon at http://www.swisstargetprediction.ch, the organism in which predictions should be made was selected (human organisms), Then click on submit button and calculations were started. The result page lists the predicted targets with their common name together with links to GeneCards (for human proteins), UniProt and ChEMBL databases (Figure 2.1).

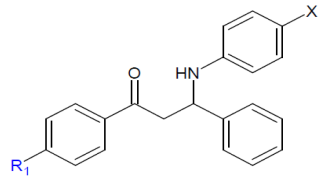


Table No. (2.1) Chemical name of the synthesized compounds

Compound No.	R_1	X	Chemical name	M. Formula	M.wt
I.	H	H	1,3-diphenyl-3-(phenylamino)propan-1-one	$C_{21}H_{19}NO$	301.38
II.	H	Br	3-[(4-bromophenyl)amino]-1,3-diphenylpropan-1-one	$C_{21}H_{18}BrNO$	380.277
III.	H	SO_2NH_2	4-[(3-oxo-1,3-diphenylpropyl)amino]benzenesulfonamide	$C_{21}H_{20}N_2O_3S$	380.46
IV.	H	COOH	4-[(3-oxo-1,3-diphenylpropyl)amino]benzoic acid	$C_{22}H_{19}NO_3$	345.391
V.	H	OCH_3	3-[(4-methoxyphenyl)amino]-1,3-diphenylpropan-1-one	$C_{22}H_{21}NO_2$	331.407
VI.	Br	H	1-(4-bromophenyl)-3-phenyl-3-(phenylamino)propan-1-one	$C_{21}H_{18}BrNO$	380.27
VII.	Br	Br	1-(4-bromophenyl)-3-[(4-bromophenyl)amino]-3-phenylpropan-1-one	$C_{21}H_{17}Br_2NO$	459.173
VIII.	Br	SO_2NH_2	4-{[3-(4-bromophenyl)-3-oxo-1-phenylpropyl]amino} benzenesulfonamide	$C_{21}H_{19}BrN_2O_3S$	459.35
IX.	Br	COOH	4-{[3-(4-bromophenyl)-3-oxo-1-phenylpropyl]amino}benzoic acid	$C_{22}H_{18}BrNO_3$	424.287
X.	Br	OCH_3	1-(4-bromophenyl)-3-[(4-methoxyphenyl)amino]-3-phenylpropan-1-one	$C_{22}H_{20}BrNO_2$	410.303

2.11. Trials

Some trials which contain certain reactants were run-out; a result of these reactions was differing according to the reaction conditions. Some of these reactions give a result, while the others failed.

2.11.1. Mannich reaction under free solvent conditions

The reactants (acetophenone or p-bromoacetophenone, sulfonamide and benzaldehyde) and catalyst (calcium chloride) were heated and stirred under reflux at 80℃ for two hours, after that the reaction mixture characterized by TLC; the result showed no formation of the product.

2.11.2. Mannich reaction with water as the solvent

In this experiment water was used as a solvent.

The reactants (acetophenone or p-bromoacetophenone, sulfonamide and benzaldehyde) and catalyst (calcium chloride) were heated and stirred under reflux at 80℃ for two hours, after that the reaction mixture characterized by TLC; the result showed formation of the product, with low yield, and couldn’t be separated.

2.11.3. Mannich reaction with ethanol as solvent and without catalyst

In this experiment ethanol was used as a solvent.

The reactants (acetophenone or p-bromoacetophenone, sulfonamide and benzaldehyde) were heated and stirred under reflux at 80℃ for two hours, after

that the reaction mixture characterized by TLC; the result showed formation of the product with low yield and couldn't separate.

2.11.4. Mannich reaction with different amines

In this experiment ethanol was used as a solvent.

The reactants (acetophenone or p-bromoacetophenone, pyrimethamine or trimethoprime or p_amino sulfonic acid and benzaldehyde) and catalyst (calcium chloride) were heated and stirred under reflux at 80℃ for 6 hours, after that the reaction mixture characterized by TLC; the results showed formation of the product but IR spectrum showed the product was not the desired product.

2.11.5. Mannich reaction with Different aldehydes

In this experiment ethanol was used as a solvent.

The reactants (acetophenone or p-bromoacetophenone, furfural aldehyde or salicylaldehyde or cinamaldehyde and aniline or sulfonamide) and catalyst (calcium chloride) in acidic media were heated and stirred under reflux at 80℃ for 6 hours, after that the reaction mixture characterized by TLC; the results showed formation of the product, with low yield, that couldn't be separated.

Chapter three
Results and discussion

3.1. Results and discussion

β -amino carbonyl compounds are very useful in pharmaceutical and other biologically related areas of chemistry, it's used for the synthesis of amino alcohols, peptides, lactams and as precursors to optically active amino acids. (Biller *et al*., 2002). One of the many synthetic routes to these compounds is the Mannich reaction. The classical synthetic methods rely on two component system using preformed electrophiles such as imines and stable nucleophiles such as enolates, enol ethers and enamine. The preferable route is the use of a one pot three components strategy which brings together three compounds under appropriate catalytic conditions (Arend, 1998). The products of Mannich reaction are mainly β -amino carbonyl compounds.

In the present work several mannich base compounds were examined, in order to select specific compounds to synthesize them. The first step was designing of 50 compounds derivatives from different amines (aniline, sulfanilamide, *p*-bromo aniline, *p*-amino benzoic acid, *o*-toluidine and *p*-anisidine), aldehydes (furfural aldehyde, salicylaldehyde, cinamaldehyde and Benzaldehyde) and different ketone (acetophenone and *p*-bromo acetophenone) (table No.3.1) using chemoinfomatic programmer (ACD/Lab); ACD/ChemSketch Freeware was used to draw chemical structures, calculation of molecular properties(molecular weight, density, molar volume, polarizability and parachor), naming structures and prediction of log P (table No.3.1).

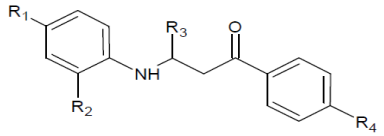


Table No. (3.1) ACD/Lab results of some β- amino acetophenone derivatives

C. No.	R_1	R_2	R_3	R_4	Log P	Molar volume ±3.0cm^3	Density ±0.06g/cm^3	Polarizability ±0.5 $10^{-24}cm^3$	Parachor ± 6.0 cm^3
1.	H	H	furan-2-yl	H	3.75+/-0.28	245.5	1.186	34.44	651.2
2.	H	H	2-hydroxyphenyl	H	3.85+/-0.27	261.1	1.215	38.24	712.2
3.	H	H	2-phenyl ethen-1-yl	H	5.29+/-0.36	287.0	1.140	41.82	762.1
4.	H	H	furan-2-yl	Br	4.52+/-0.39	261.7	1.414	37.49	701.7
5.	H	H	2-hydroxyphenyl	Br	4.62+/-0.38	277.3	1.428	41.29	762.7
6.	H	H	2-phenyl ethen-1-yl	Br	6.06+/-0.41	303.2	1.339	44.87	812.6
7.	SO_2NH_2	H	furan-2-yl	H	2.24+/-0.31	274.5	1.349	39.14	765.7
8.	SO_2NH_2	H	2-hydroxyphenyl	H	2.34+/-0.30	290.1	1.366	42.72	825.7
9.	SO_2NH_2	H	2-phenyl ethen-1-yl	H	3.78+/-0.37	316.0	1.286	45.75	878.2
10.	SO_2NH_2	H	furan-2-yl	Br	3.00+/-0.42	290.6	1.545	42.20	816.8
11.	SO_2NH_2	H	2-hydroxyphenyl	Br	3.10+/-0.41	306.3	1.55	45.78	876.7
12.	H	CH_3	phenyl	Br	5.81+/- 0.37	295.2	1.335	42.45	785.4
13.	H	CH_3	phenyl	H	5.05+/- 0.27	279.0	1.130	39.40	734.9
14.	SO_2NH_2	H	2-phenyl ethen-1-yl	Br	4.54+/- 0.42	332.1	1.461	48.81	929.3
15.	SO_3H	H	phenyl	Br	4.31+/- 0.41	301.7	1.525	44.35	848.8
16.	SO_3H	H	phenyl	H	3.54+/- 0.29	285.5	1.335	41.29	797.7
17.	Br	H	phenyl	Br	6.52+/- 0.47	295.1	1.555	43.59	798.2
18.	Br	H	phenyl	H	5.76+/- 0.38	278.9	1.363	40.54	747.7
19.	COOH	H	phenyl	Br	5.46+/- 0.41	291.4	1.455	43.29	809.8
20.	COOH	H	phenyl	H	4.70+/- 0.29	275.2	1.254	40.24	759.4
21.	OCH_3	H	phenyl	Br	5.17+/- 0.41	302.9	1.354	43.19	804.4
22.	OCH_3	H	phenyl	H	4.40+/- 0.28	286.7	1.155	40.14	753.9
23.	H	H	phenyl	Br	5.35+/-0.37	278.9	1.363	40.54	747.7
24.	H	H	phenyl	H	4.59+/-0.27	262.7	1.146	37.49	697.2

Continue table No. (3.1)

25.	SO_2NH_2	H	phenyl	Br	3.84+/-0.41	307.9	1.491	45.18	861.5
26.	SO_2NH_2	H	phenyl	H	3.07+/-0.28	291.7	1.304	42.12	810.5
27.	SO_3H	H	2-phenyl ethen-1-yl	Br	5.01+/- 0.42	326.0	1.491	47.98	916.5
28.	SO_3H	H	2-phenyl ethen-1-yl	H	4.25+/- 0.37	309.8	1.315	44.92	865.5
29.	Br	H	2-phenyl ethen-1-yl	Br	7.22+/- 0.48	319.4	1.518	47.92	863.1
30.	Br	H	2-phenyl ethen-1-yl	H	6.46+/- 0.41	303.2	1.339	44.87	812.6
31.	COOH	H	2-phenyl ethen-1-yl	Br	6.17+/- 0.42	315.7	1.426	47.62	874.7
32.	COOH	H	2-phenyl ethen-1-yl	H	5.40+/- 0.37	299.5	1.239	44.57	824.2
33.	OCH_3	H	2-phenyl ethen-1-yl	Br	5.87+/- 0.41	327.2	1.333	47.52	869.3
34.	OCH_3	H	2-phenyl ethen-1-yl	H	5.11+/- 0.37	311.0	1.149	44.47	818.8
35.	SO_3H	H	furan-2-yl	Br	3.47+/- 0.42	284.5	1.582	41.37	804.0
36.	SO_3H	H	furan-2-yl	H	2.70+/- 0.32	268.3	1.384	38.31	753.0
37.	Br	H	furan-2-yl	Br	5.68+/- 0.48	277.9	1.615	40.54	752.2
38.	Br	H	furan-2-yl	H	4.92+/- 0.40	261.7	1.414	37.49	701.7
39.	COOH	H	furan-2-yl	Br	4.63+/- 0.42	274.2	1.510	40.23	763.8
40.	COOH	H	furan-2-yl	H	3.86+/- 0.32	258.0	1.299	37.19	713.3
41.	OCH_3	H	furan-2-yl	Br	4.33+/- 0.41	285.7	1.400	40.13	758.4
42.	OCH_3	H	furan-2-yl	H	3.57+/- 0.30	269.5	1.192	37.09	707.9
43.	SO_3H	H	2-hydroxyphenyl	Br	3.57+/- 0.41	300.1	1.586	44.95	864.0
44.	SO_3H	H	2-hydroxyphenyl	H	2.81+/- 0.30	283.9	1.399	41.89	813.0
45.	Br	H	2-hydroxyphenyl	Br	5.78+/- 0.47	293.5	1.618	44.33	813.2
46.	Br	H	2-hydroxyphenyl	H	5.02+/- 0.39	277.3	1.428	41.29	762.7
47.	COOH	H	2-hydroxyphenyl	Br	4.73+/- 0.41	289.9	1.518	44.03	824.9
48.	COOH	H	2-hydroxyphenyl	H	3.96+/- 0.30	273.7	1.320	40.98	774.4
49.	OCH_3	H	2-hydroxyphenyl	Br	4.43+/- 0.41	301.3	1.414	43.93	819.4
50.	OCH_3	H	2-hydroxyphenyl	H	3.67+/- 0.29	285.2	1.218	40.88	768.9

The relationship of these properties between the different compounds (figure1.1-1.5) were studied by Microsoft excel programmer.

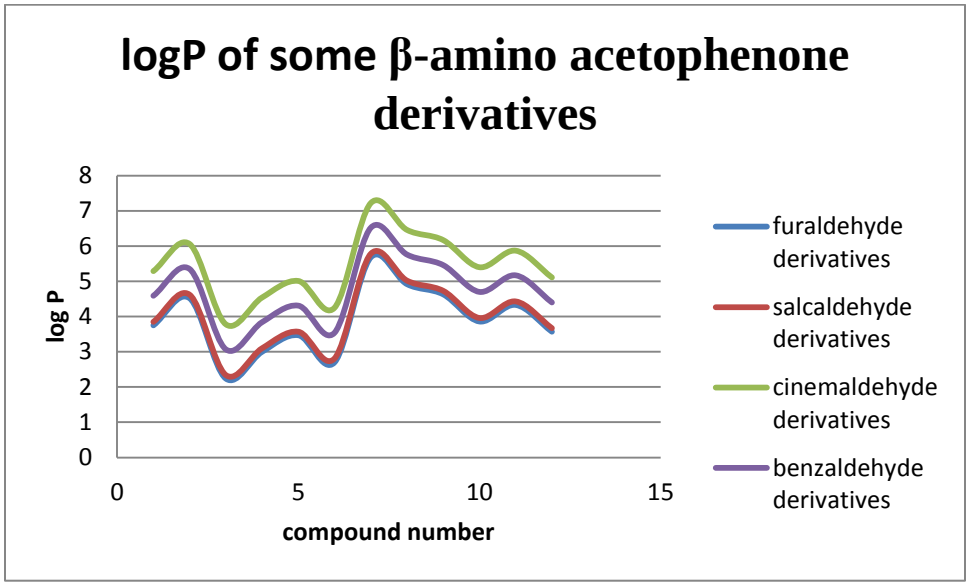


Figure (3.1) LogP of some β-amino acetophenone derivatives

From the above figure cinemaldehyde derivatives have a log P value greater than those of other aldehydes derivatives, furfural aldehyde derivatives and salicylaedehyde derivatives have a same value of log P. 2-phenyl ethen-1-yl have high effect on the log P value of the product, the effect of furan-2-yl and 2-hydroxyphenyl groups on the log P value of the product are similar. Phenyl had intermediate effect compeer between 2-phenyl ethen-1-yl, furan-2-yl, and 2-hydroxyphenyl groups.

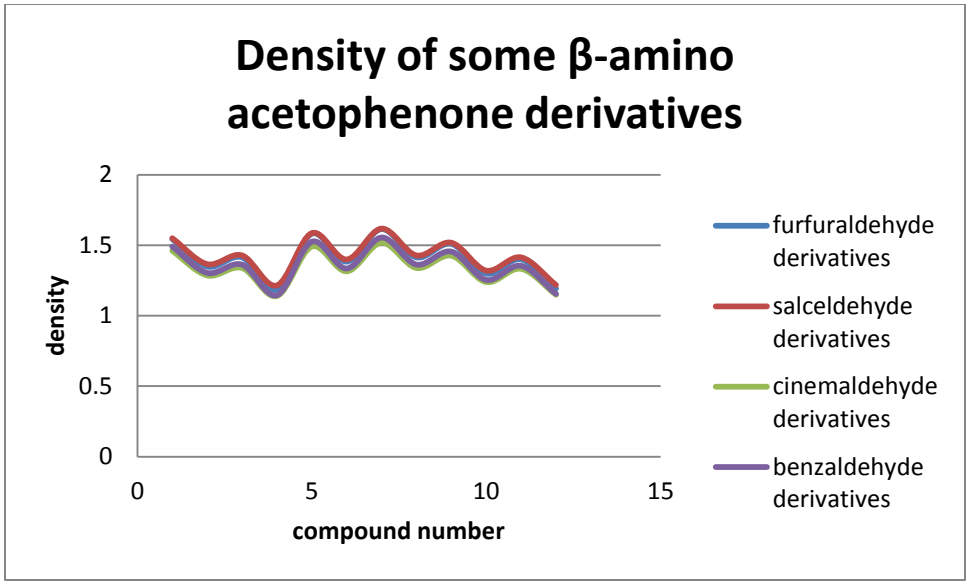


Figure (3.2) Density of some β-amino acetophenone derivatives

From the above figure all compounds have same density but salceldehyde derivatives slightly differ.

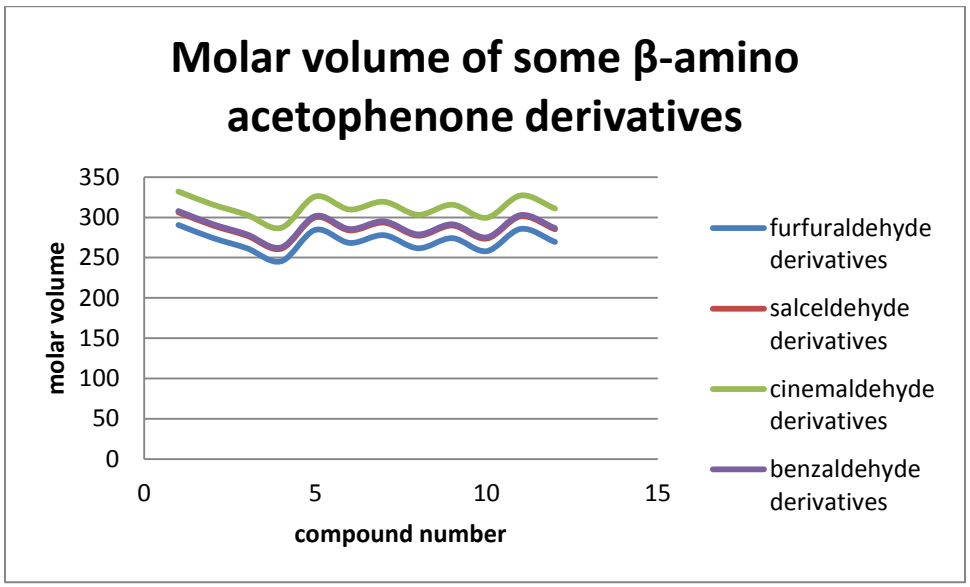


Figure (3.3) Molar volume of some β-amino acetophenone derivatives

From above figure cinemaldehyde derivatives have high molar volume because of increase of the number of atoms, salceldehyde and Benzaldehyde derivatives have a

same value that means that hydroxyl group on salceldehyde does not affect the molar volume.

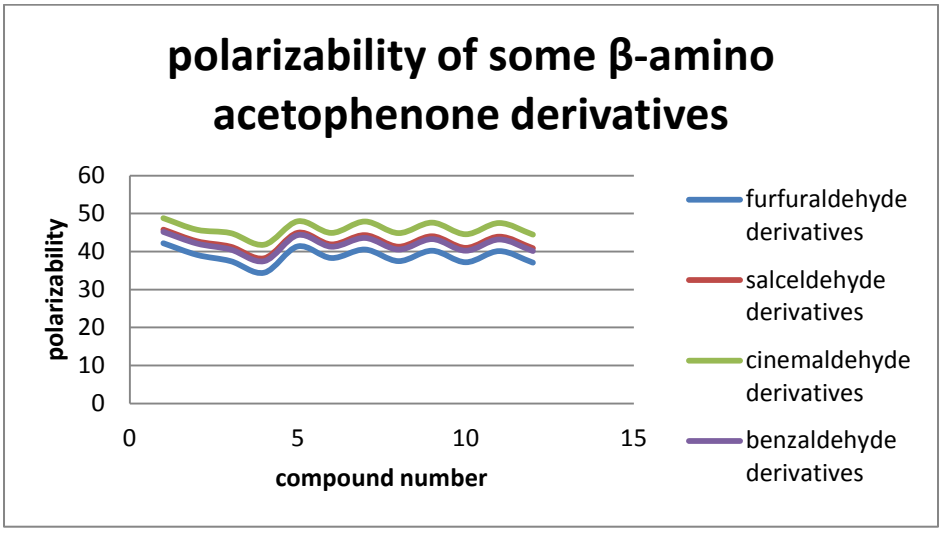


Figure (3.4) Polarizability of some β-amino acetophenone derivatives

Polarizability figure typical with molar volume figure, cinemaldehyde derivatives have high polarizability. Salceldehyde and Benzaldehyde derivatives have same values that mean hydroxyl group on salceldehyde not affect the polarizability.

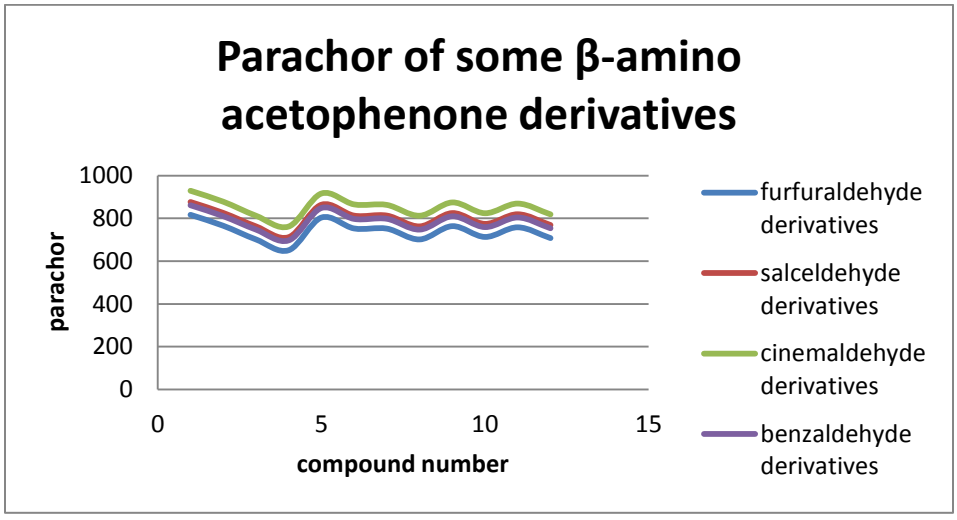


Figure (3.5) Parachor of some β-amino acetophenone derivatives

Parachor figure is typical with molar volume figure and polarizability figure. cinemaldehyde derivatives have high parachor. Salceldehyde and Benzaldehyde derivatives have same values that mean hydroxyl group on salceldehyde does not affect the parachor.

Selection of compounds

Log*P*

In drug design compounds with high log P values cause poor absorption or permeation. So compounds were selected with low log P value (benzaldehyde derivatives, salceldehyde derivatives, and furfural aldehyde derivatives).

Molar volume and polarizability

Compounds were selected with high molar volume and large polarizability (benzaldehyde derivatives, and salceldehyde derivatives).

Effect of substituent

Aromatic aldehyde (cinemaldehyde) with an effective conjugation system forms stable imine so the final product cannot form. Aromatic aldehyde (salcildehyde) and amine (ortho toluidine) with ortho substituent cannot form final product because of steric hindrance.

From the above study it is conclude that benzaldehyde derivatives are the best selection.

Correlation the structure properties of the benzaldehyde derivatives

Ten compounds derivatives from benzaldehyde (table No. 1.2) were selected.

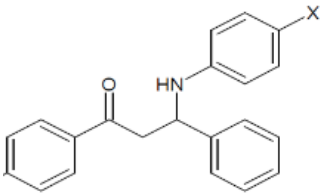


Table (3.2.A): ACD/Lab results of some benzaldehyde derivatives

No.	X	Log P	Molar volume ±3.0cm^3	Density ±0.06g/cm^3	Polarizabilit y ±0.5 10^{-24}cm^3
1.	Br	5.76	278.9	1.363	40.54
2.	COOH	4.70	275.2	1.254	40.24
3.	H	4.59	262.7	1.146	37.49
4.	OCH_3	4.40	286.7	1.155	40.14
5.	SO_2NH_2	3.07	291.7	1.304	42.12

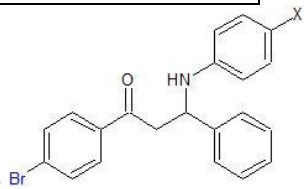


Table (3.2.B): ACD/Lab results of some benzaldehyde derivatives

No.	X	Log P	Molar volume ±3.0cm^3	Density ±0.06g/cm^3	Polarizabilit y ±0.5 10^{-24}cm^3
1.	Br	6.52	295.1	1.555	43.59
2.	COOH	5.46	291.4	1.455	43.29
3.	H	5.35	278.9	1.363	40.54
4.	OCH_3	5.17	302.9	1.354	43.19
5.	SO_2NH_2	3.84	307.9	1.491	45.18

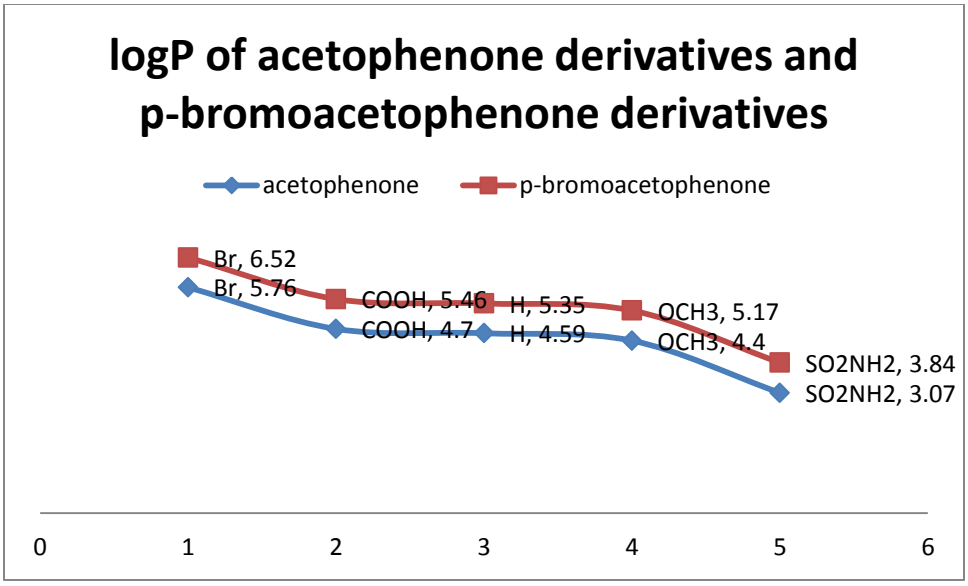


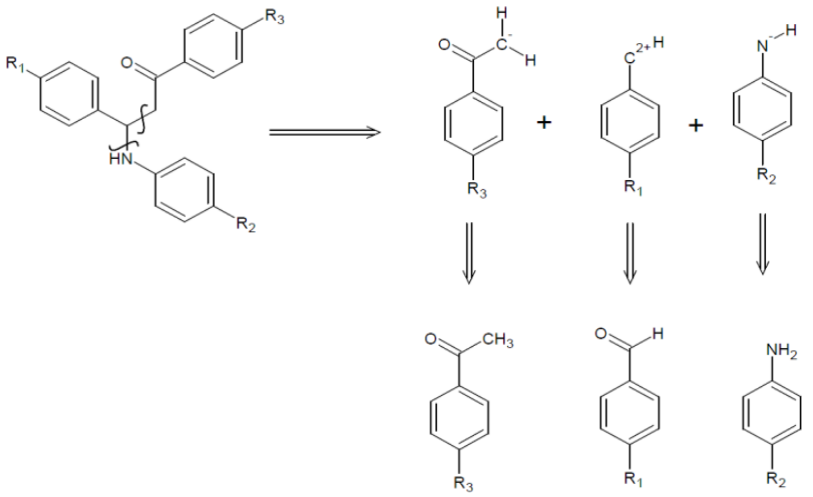
Figure (3.6) relationship between logP of p-bromo actophenone derivatives and acetophenone derivatives

From the above tables (No.(3.2.A) and (3.2.B)), and figure (3.6) bromide extremely increases log P value of the products compared with carboxyl group; methoxy and sulfonamide groups decrease log P values of the products but the effect of sulfonamide is very large; *p*- bromo acetophenone derivatives have a log *P* value greater than those of acetophenone derivatives; Bromine atom increases the log *P* value.

The decreased electrophilicity of imines (intermediates compounds) is readily accounted for by the lower electronegativity of nitrogen compared with that of oxygen. As a result of the reduced electronegativity of the heteroatom, the double bond in an imine is less polarised. There is therefore a weaker dipole moment across an imine than across the corresponding carbonyl group. There is therefore less δ+

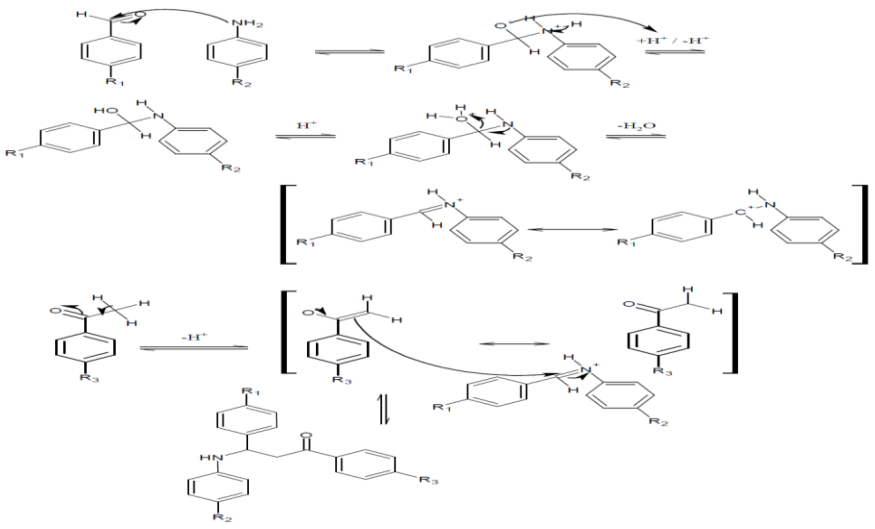
charge at the imine carbon atom which makes it less electrophilic. Brome (electron withdrawing group) increases the reactivity of intermediate compound toward electrophilic attack.

The designing of the required compounds were planned by use of disconnection approach and retro synthetic analysis (RSA). According to retro synthetic analysis protocols the disconnections occur at the bond between carbon and nitrogen and the bond between carbon and carbon giving the corresponding synthons (scheme 3.1).



Scheme 3. 1 Retro synthetic analysis of β-amino carbonyl compounds

It was clearly seen that the target molecule constituted three starting materials aromatic amines, aromatic aldehydes and aromatic ketones. The possible mechanism of the reaction is nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base, which reacts in the second step as nucleophile with a compound containing an acidic proton (enol) scheme 3.2.



Scheme 3. 2. Mechanism of formation of *β*-amino carbonyl compounds

Mannich reaction of aromatic amines, aromatic aldehydes and aromatic ketones have been catalyzed by organic and mineral acid such as proline, acetic acid and dodecyl benzene sulfonic acid; however, most of these methods suffer from drawbacks such as use of corrosive reagent, expensive and large amount of catalyst, long reaction time and difficulty in product separation which limit their use in synthesis of complex molecules. Recent achievements in the efficient construction of these molecules include the development of various catalysts such as lewis acid catalysts, bronsted acid catalysts and lewis base catalysts to facilitate Mannich reaction (Dabiri *et al.*, 2011).

In the present work calcium chloride, being lewis base, is inexpensive, nontoxic to the environment and easily available catalyst, that is efficiently catalysis three components to synthesize *β*-amino carbonyl compounds, via one pot condensation of aromatic ketones, aromatic aldehydes and aromatic amines, in short reaction time (2h)

with temperature adjusted at 80°C and with mechanical stirring in the presence of one drop HCl in ethanol as shown in schemes 2.1 and 2.2 and table (3.3).

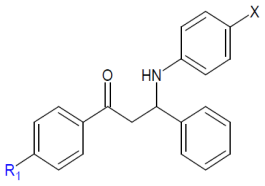


Table (3.3): Reaction conditions of *β*- amino carbonyl compounds

Compound No.	R_1	X	Reaction time hours	Reaction tep °C
I.	H	H	2	80
II.	H	Br	2	80
III.	H	SO_2NH_2	2	80
IV.	H	COOH	2	80
V.	H	OCH_3	2	80
VI.	Br	H	2	80
VII.	Br	Br	2	80
VIII.	Br	SO_2NH_2	2	80
IX.	Br	COOH	2	80
X.	Br	OCH_3	2	80

Aromatic amines bearing various functional groups (Br, COOH, OCH_3 and SO_2NH_2), table No (3.4) all react to produce the corresponding *β*- amino acetophenone derivatives with yield percentage 41% to 98%. *β*- amino *p*-bromo acetophenone derivatives yielded higher percentage than *β*- amino acetophenone derivatives as electron withdrawing group increases reactivity of the formed enolate, table No (3.4). The purity of the compound was established by presence of single spot in TLC plate (silica gel), table No (3.4); solvent system used was Chloroform: methanol (95:5); Rf value varied from 0.2 to 0.97. The melting points of synthesized compounds varied from 98°C to 198°C, table No (3.4).

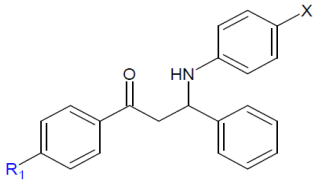


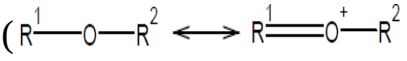
Table (3.4): Physical properties of *β*- amino acetophenone derivatives products

Compound No.	R_1	X	Yield g	Yield %	m.p ℃	Rf
I.	H	H	1.29	86	166-170 (Lit/169-170, Kulkarni *et al.*, 2011)	0.21
II.	H	Br	1.33	70	129-133 (Lit/130-131, Kulkarni *et al.*, 2011)	0.968
III.	H	SO_2NH_2	1.48	78	159-163	0.20
IV.	H	COOH	1.46	86	186-190	0.571
V.	H	OCH_3	0.67	41	162-166 (Lit/163-164, Kulkarni *et al.*, 2011)	0.46
VI.	Br	H	1.86	98	98-102	0.97
VII.	Br	Br	1.61	70	154-158	0.952
VIII.	Br	SO_2NH_2	2.14	93	151-156	0.959
IX.	Br	COOH	1.62	81	194-198	0.428
X.	Br	OCH_3	0.99	47	156-160	0.751

*Mobile phase: Chloroform: Methanol (9.50: 0.50)

* Recrystallize solvent: Ethanol

The structures of newly synthesized compounds have been elucidated by physico-chemical methods using IR and ^{1}H-NMR spectral techniques.

The IR spectrum of Mannich bases (I-X), table (3.5) and figures (A.1, A.3,…,A.19) (appendix), showed the appearance of single medium to intense sharp absorption band attributed to N-H bond stretching vibration at 3296-3386.77 cm^{-1} region confirmed by the presence of medium and strong peak at 1525 -1600 cm^{-1} region for N-H bending frequency. Peaks at (3024-3083.96) cm^{-1} and 698.18 -862.12 cm^{-1} region indicate the presence of C-H stretching vibration and bending in aromatic system; strong peak at (1604-1677) cm^{-1} for C=O in ketone its shift to the lower value cause by conjugation with aromatic system; peak at 2918-2955 cm^{-1} indicate the presence of C-H stretching vibration in aliphatic system; peak at (1448-1460) cm^{-1} indicate the presence of CH_2 bonds bending frequency. Appearance of peaks at (1323-1330.76) cm^{-1} and at (1149-1151.42) cm^{-1} region in Mannich bases III and VIII table (3.5) figures (A.5) and (A.15) indicate the presence of symmetrical and asymmetrical stretching vibration of SO_2 group, strong bands at (1249 and 1033) cm^{-1} in Mannich bases V and X figures (A.9) and (A.19) indicate the presence of C-O-C (aryl alkyl ether) an a symmetric and a symmetric stretching vibration, the shift in the asymmetric stretching frequencies in aryl ethers cause of resonance increased double bond character (), strong

bands at 1674 cm^{-1} in Mannich bases IV and IX figures (A.13) and (A.17) indicate the presence of (C=O) in carboxylic acid.

All this bands confirm the correct formation of the product.

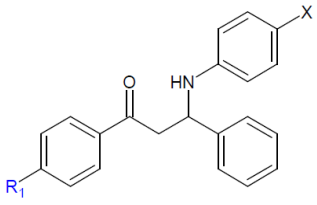


Table (3.5): Infrared absorption frequencies of *β*- amino acetophenone derivatives products

Compound No.	R_1	X	C-H st-vib (Aliphatic) (cm^{-1})	C-H st-vib (Aromatic) (cm^{-1})	C-H bend (Aromatic) (cm^{-1})	C=O ketone (cm^{-1})	N-H str-vib (cm^{-1})	N-H bend (cm^{-1})	CH_2 bend (cm^{-1})	Over tone (cm^{-1})	Other (cm^{-1})
I.	H	H	2918.10	3024	862.12	1670.24	3384.89	1600.81	1448.44	1961.47, 1893.97, 1814.89	_
II.	H	Br	2935.46	3020.32	802	1666.38	3371.34	1596.95	-	-	-
III.	H	SO_2NH_2	-	3021.6	835.12	1668.31	3296.12	1581.52	1452.3	1976.9, 1907.47	1330.76, 1151.42 (SO_2)
IV.	H	COOH	2950	3066.61	698.18	1660	3359.77	-	1450	1890.11, 1920.97, 1955.68	1674 (C=O Acid)
V.	H	OCH_3	2954.74	3058	-	1668	3371.34	-	1446	-	1033, 1218 (C-O)
VI.	Br	H	2920.03	3024.18	823.55	1668.31	3377.12	1598.88	1448.4	1961.47, 1919.04, 1820.68, 1770.53	-
VII.	Br	Br	2950.89	3028.03	810.05	1677.95	3359.77	1585.38	1454.23	-	-
VIII.	Br	SO_2NH_2	2921.96	3083.96	817.76	1664.45	3386.77	1525.59	1450.37	1922.9	1323.03, 1149.5 (SO_2)
IX.	Br	COOH	2950	3066.61	698.18	1604	3367.48	1585.38	-	1955.68, 1920.97	1674.10 (C=O Acid)
X.	Br	OCH_3	2954.74	3055	-	1677	3382	-	1460	-	1029, 1249 (C-O)

The ^{1}H NMR spectrums of synthesized Mannich bases (I-X) figures (A.2, A.4, …, A.20) (appendix), table(3.5) showed double doublet at 2.50 ppm (d d, 1H) assigned for the proton from methine group (C**H**) neighboring to the aromatic ring and the secondary amino group, while the two double doublets at (3.20-3.33) ppm (d d, 2H) assigned for methylene protons (C$\mathbf{H_2}$) neighboring to the carbonyl group, the broad and weak signal at range (4.80 to 5.10) ppm (s, 1H) is assigned for (N**H)** proton, the signals in the aromatic region of the spectra, difficult to ascribe to a particular proton because of their mingling, are presented as a multiplet at range (6.00 to 8.60) ppm; however, their number always agree with the compound's structure. Single (S, 1H) intense peak at 3.75 ppm in H^{1}NMR spectrums of Mannich bases (V) and (X) figures (A.10) and (A.20) account for methyl protons. Peak at 12.00 ppm in ^{1}HNMR spectrum of Mannich base (IX) figure (A.18) characteristic of carboxylic acid proton (COO**H**). Peak at 5.80 ppm in H^{1}NMR spectrums of Mannich bases (III) and (VIII) figures (A.6) and (A.16) account for $SO_2N\mathbf{H_2}$ protons.

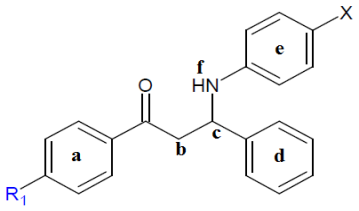


Table (3.4): ^{1}H NMR Chemical shift of *β*- amino acetophenone derivatives products

Compound No.	R_1	X	Chemical shift(intensity, multiplicity) ppm				
			a, d, e (m)	b(two(d d))	c(d d)	f(s)	Other (s)
I.	H	H	6.30-8.00	3.20-3.30	2.50	5.00	-
II.	H	Br	6.50-8.00	3.20-3.30	2.50	5.00	-
III.	H	SO_2NH_2	6.50-8.51	3.20-3.30	2.50	5.00	5.80
IV.	H	COOH	6.50-8.00	3.20-3.30	2.50	5.00	5.80
V.	H	OCH_3	6.50-8.00	3.20-3.30	2.50	4.80	3.75
VI.	Br	H	6.20-8.20	3.20-3.30	2.50	5.00	-
VII.	Br	Br	6.50-8.00	3.20-3.30	2.50	4.80	-
VIII.	Br	SO_2NH_2	6.50-8.00	3.20-3.30	2.50	5.00	5.80
IX.	Br	COOH	6.50-8.00	3.20-3.30	2.50	5.00	-
X.	Br	OCH_3	6.50-8.00	3.20-3.30	2.50	4.80	3.75

Swiss target prediction result in below page (figure 2.1), showed the list of predicted targets for the query molecule. Targets were ranked according to their scores. Links to GeneCards (under 'Common name' column), UniProt and ChEMBL (provided for the ligands and the similarity with the query molecule) were provided. Green bars indicate the estimated probability of a protein. The sixth column (# sim cmpds 3D/2D) showed the number of ligands of the predicted target or its homologs that display similarity with the query molecule based on either 2D or 3D similarity measures.

Functional assay results in this database indicate that Mannich bases (I-X) except (III and VIII) figure (A.21-A.30) (appendix) are active on estrogen receptor and microtubule-associated protein tau (associated with Alzheimer disease) with high probability.

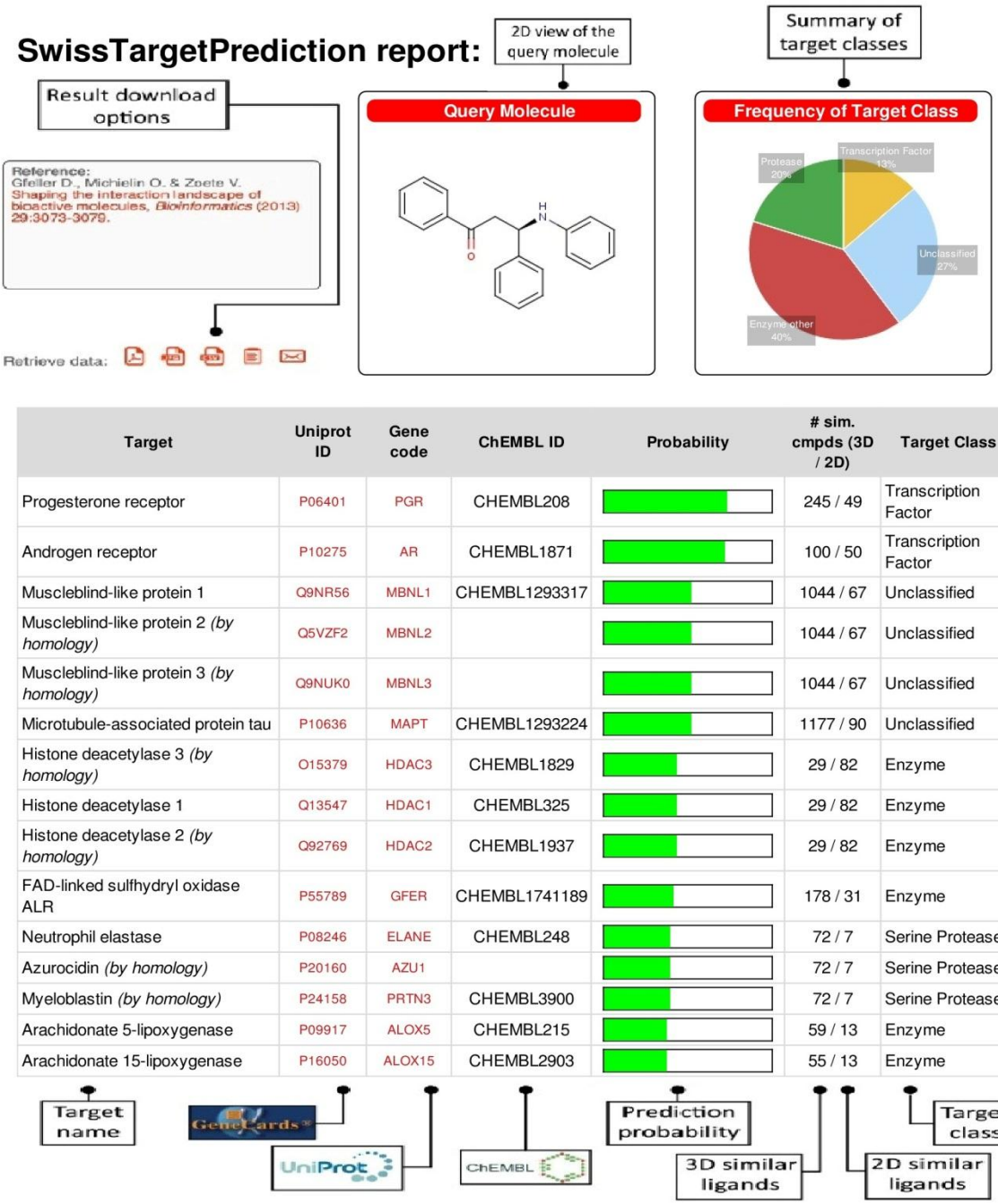


Figure (3.7) Swiss target prediction result page

Conclusion and recommendation

In the present study ten compounds of β-aminoacetophenone derivatives were synthesized by the condensation of ketone (acetophenone, *p*-bromoacetophenone) with different aromatic amines and benzaldehyde and calcium chloride as a catalyst. The structures of synthesized compounds were confirmed by various spectral tools (IR and ^{1}H NMR).

The percentage, R_f value and the melting point of the synthesized compounds were calculated.

Log P, structure name, molecular weight and molecular formula of synthesized compounds were calculated by ACD/ Lab programme.

Recommendations:

The synthesized Mannich bases could be extended to evaluate their biological and pharmacological activities.

Benzaldehyde may be replaced by furfural aldehyde or any aldehyde to obtain another series of Mannich bases.

The effect of the log P value of the solvent on the reaction rate (reactivity of the substrate and stability of the intermediate compounds) could be studied.

Application of Mannich bases as stationary phase in affinity chromatography.

Chapter four
Reference

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Appendix

Spectral data:

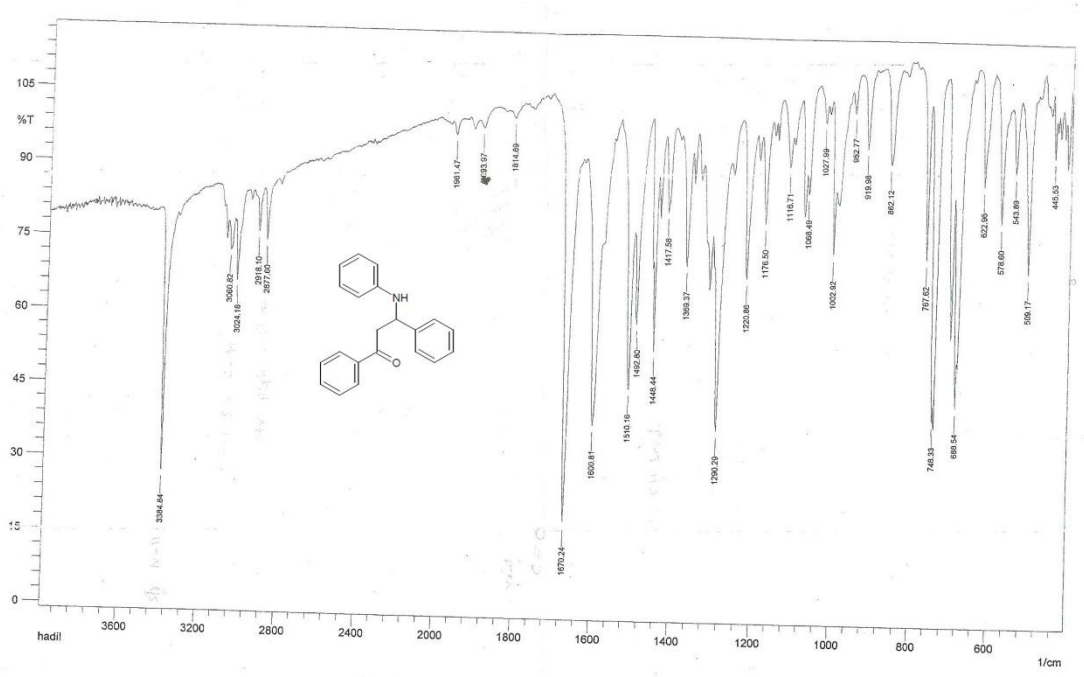


Figure (A.1) IR spectrum of the Mannich base (I)

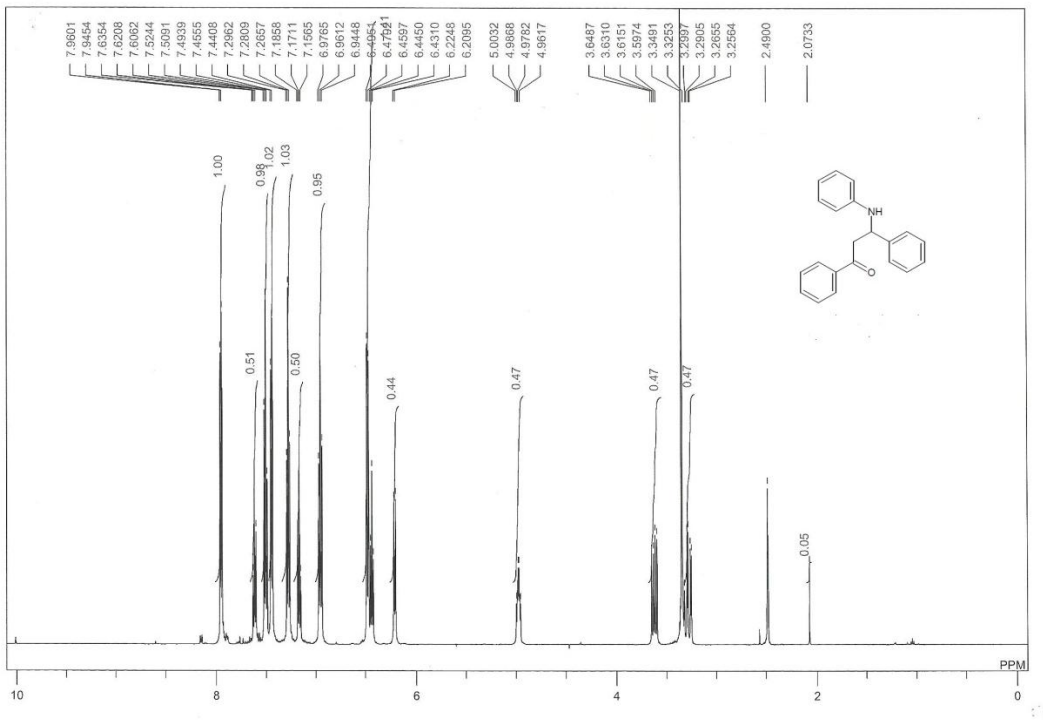


Figure (A.2) ^{1}HNMR spectrum of the Mannich base (I)

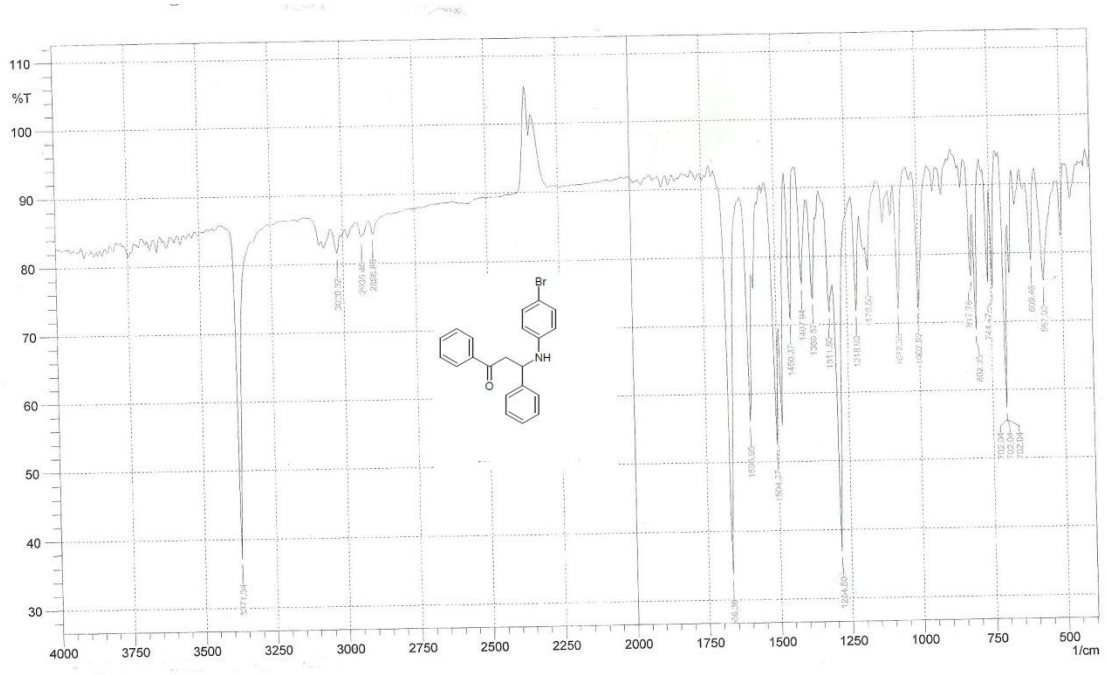


Figure (A.3) IR spectrum of the Mannich base (II)

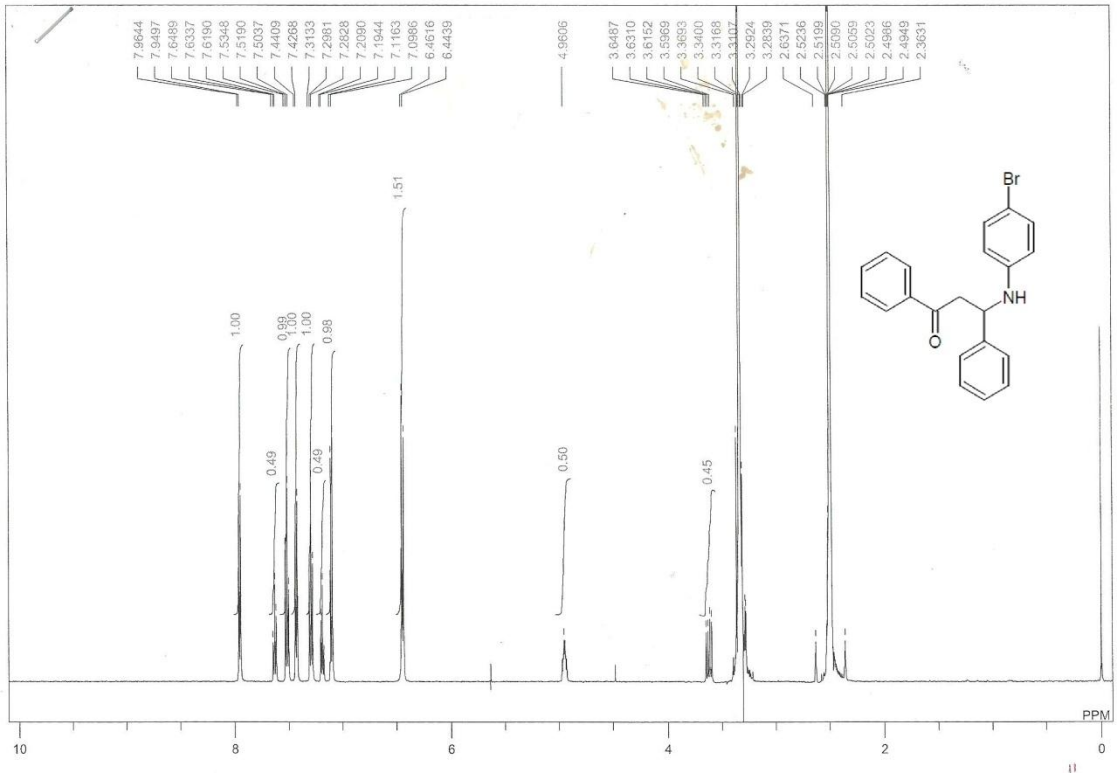


Figure (A.4) ^{1}HNMR spectrum of the Mannich base (II)

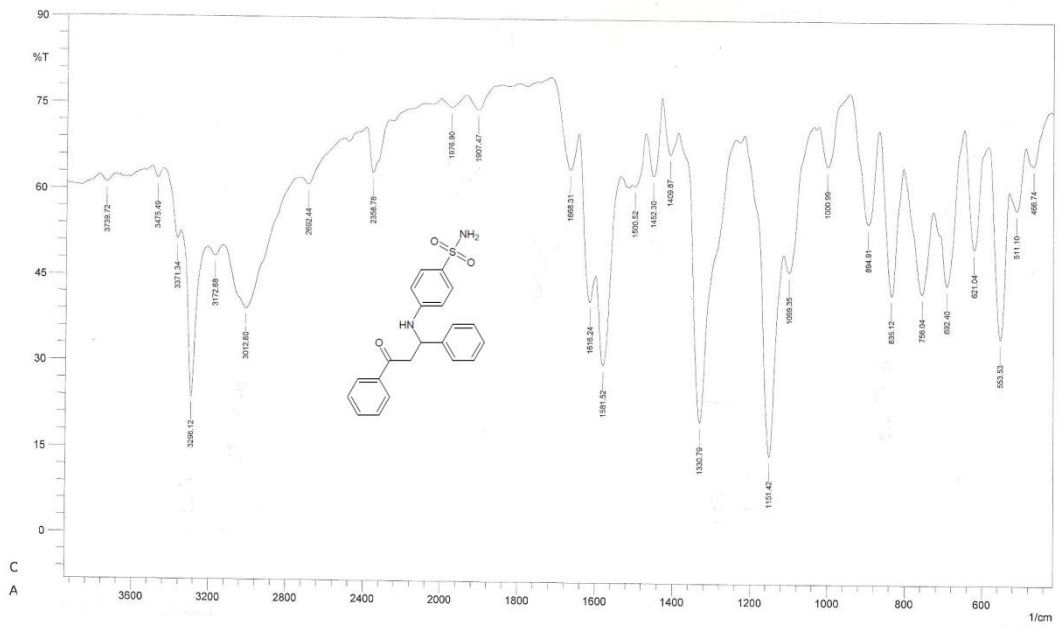


Figure (A.5) IR spectrum of the Mannich base (III)

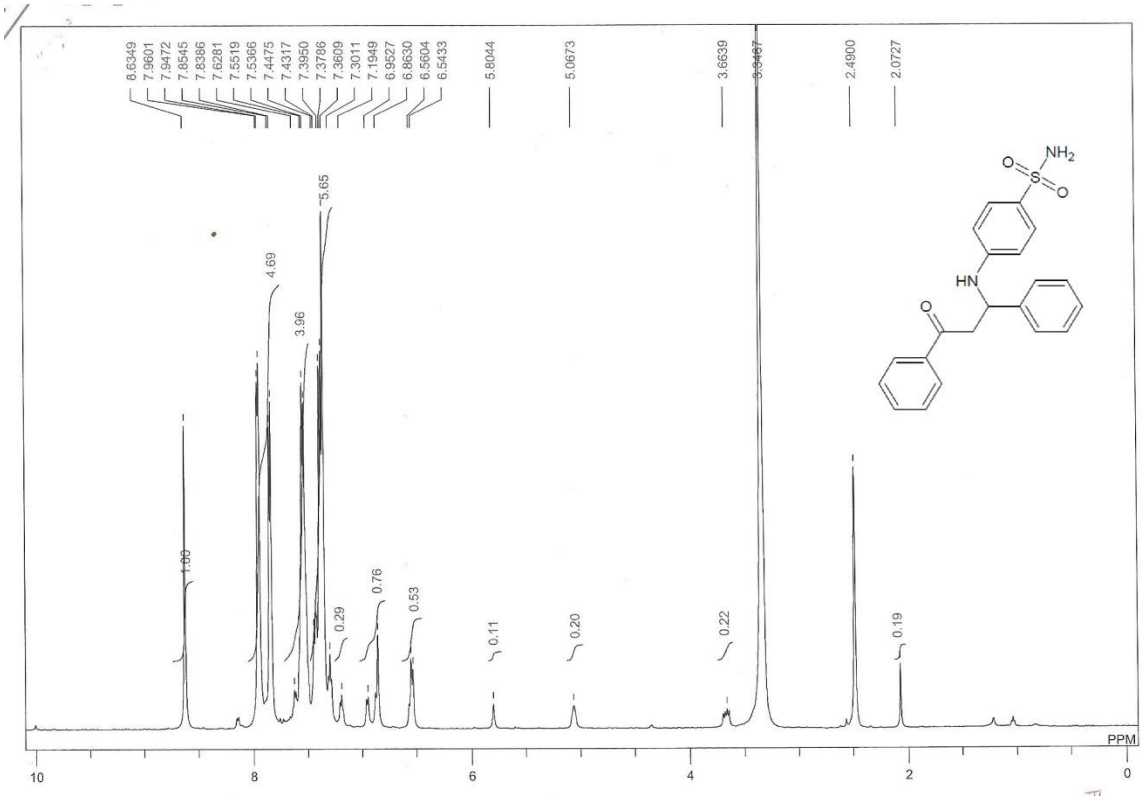


Figure (A.6) ^{1}HNMR spectrum of the Mannich base (III)

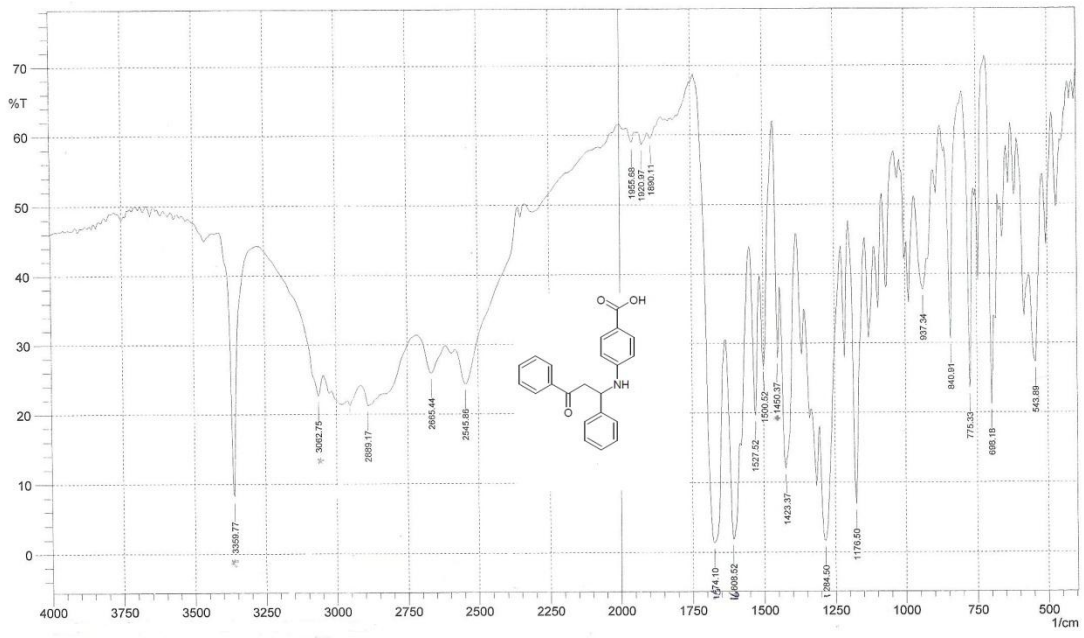


Figure (A.7) IR spectrum of the Mannich base (IV)

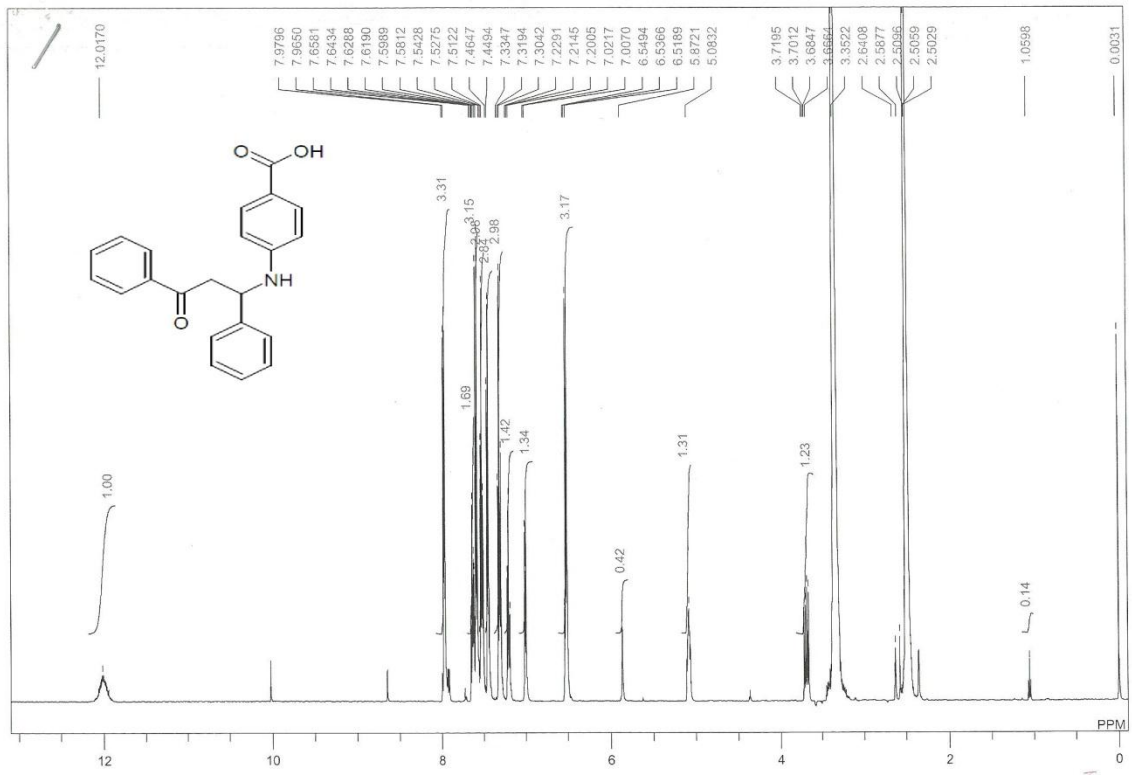


Figure (A.8) ^{1}HNMR spectrum of the Mannich base (IV)

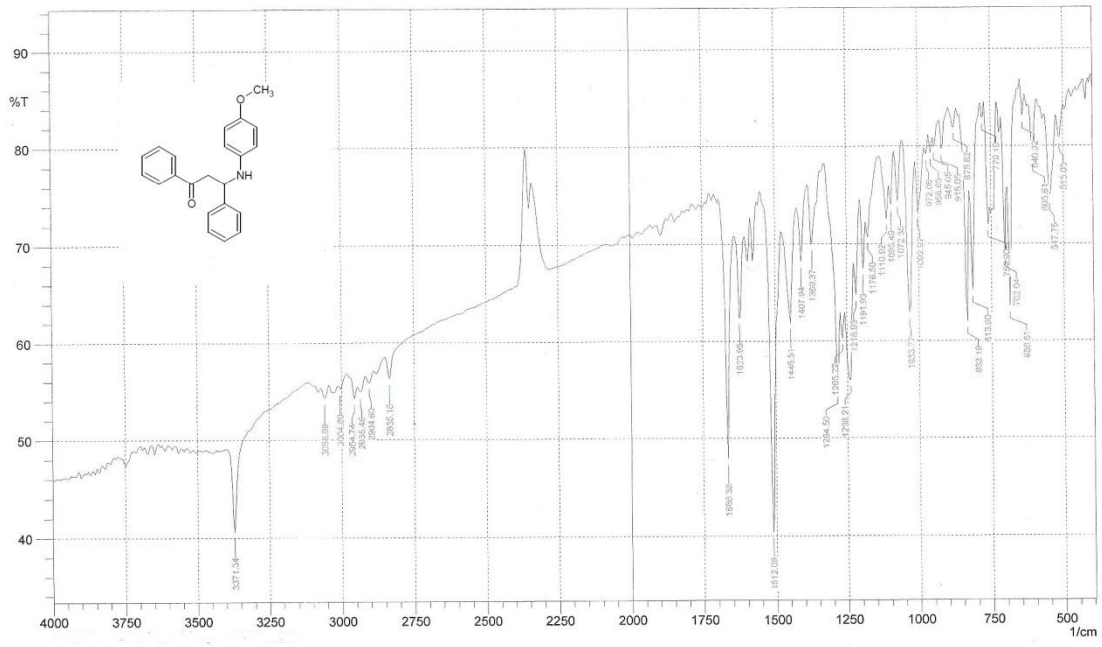


Figure (A.9) IR spectrum of the Mannich base (V)

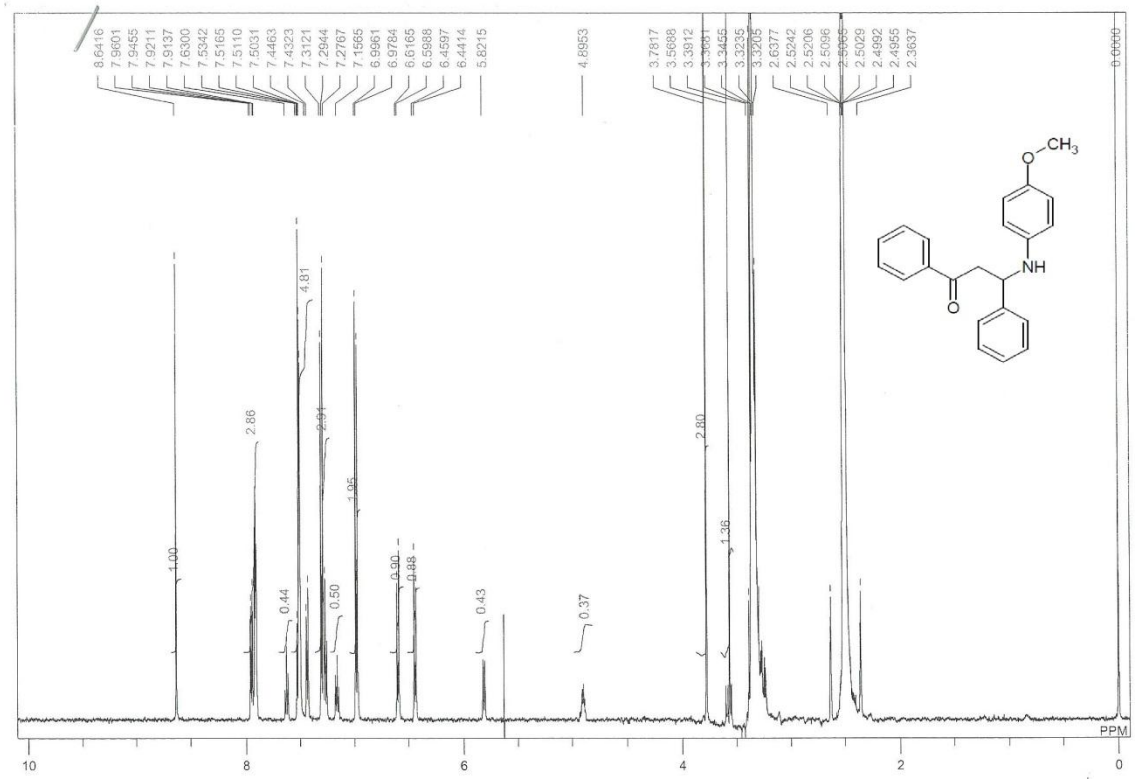


Figure (A.10) ^{1}HNMR spectrum of the Mannich base (V)

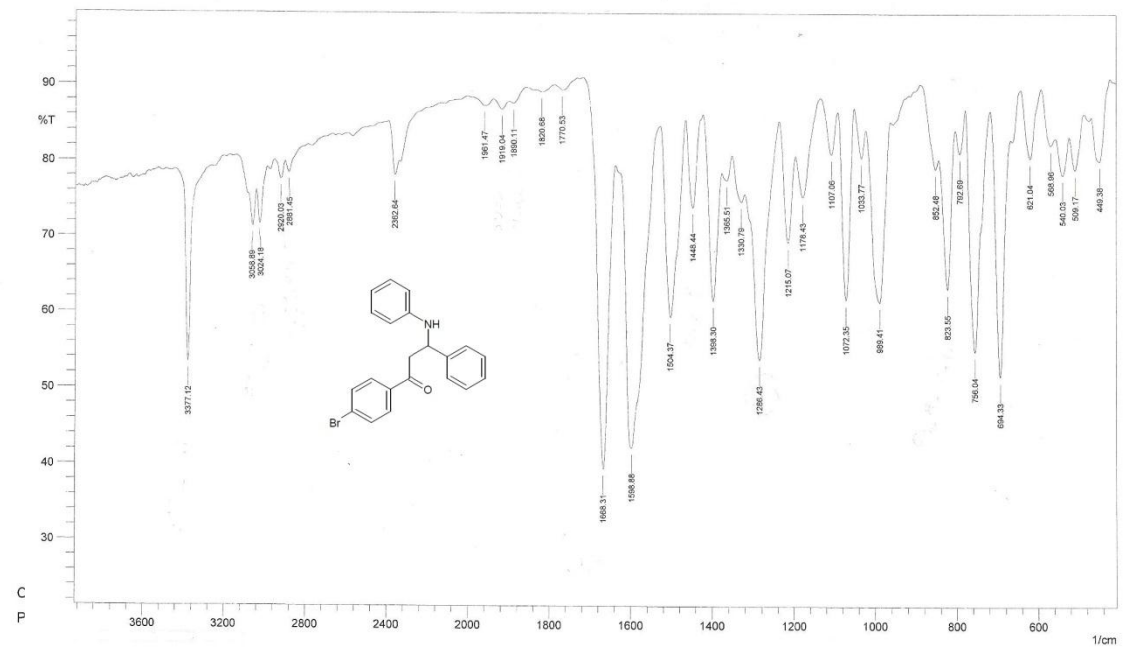


Figure (A.11) IR spectrum of the Mannich base (VI)

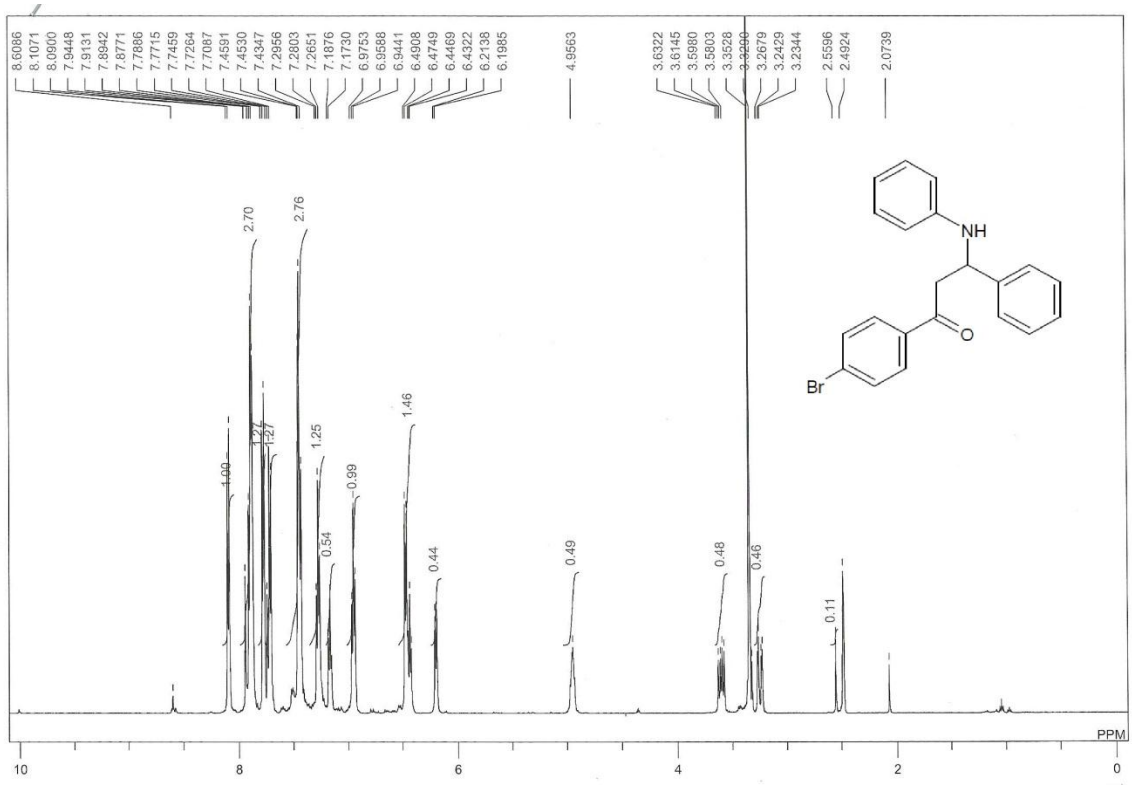


Figure (A.12) ^{1}HNMR spectrum of the Mannich base (VI)

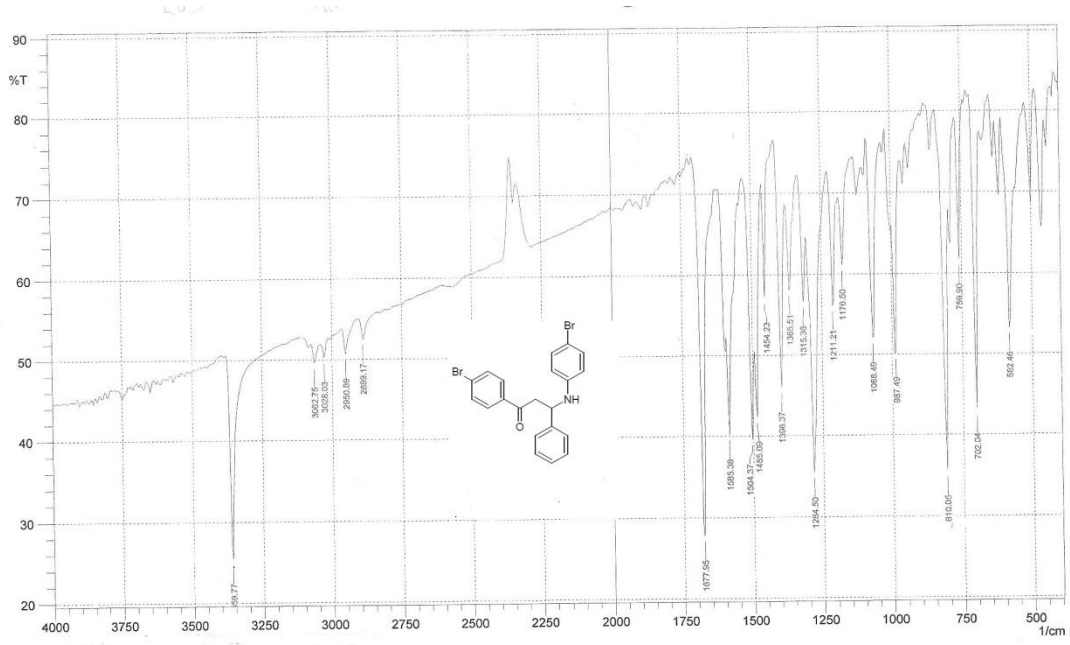


Figure (A.13) IR spectrum of the Mannich base (VII)

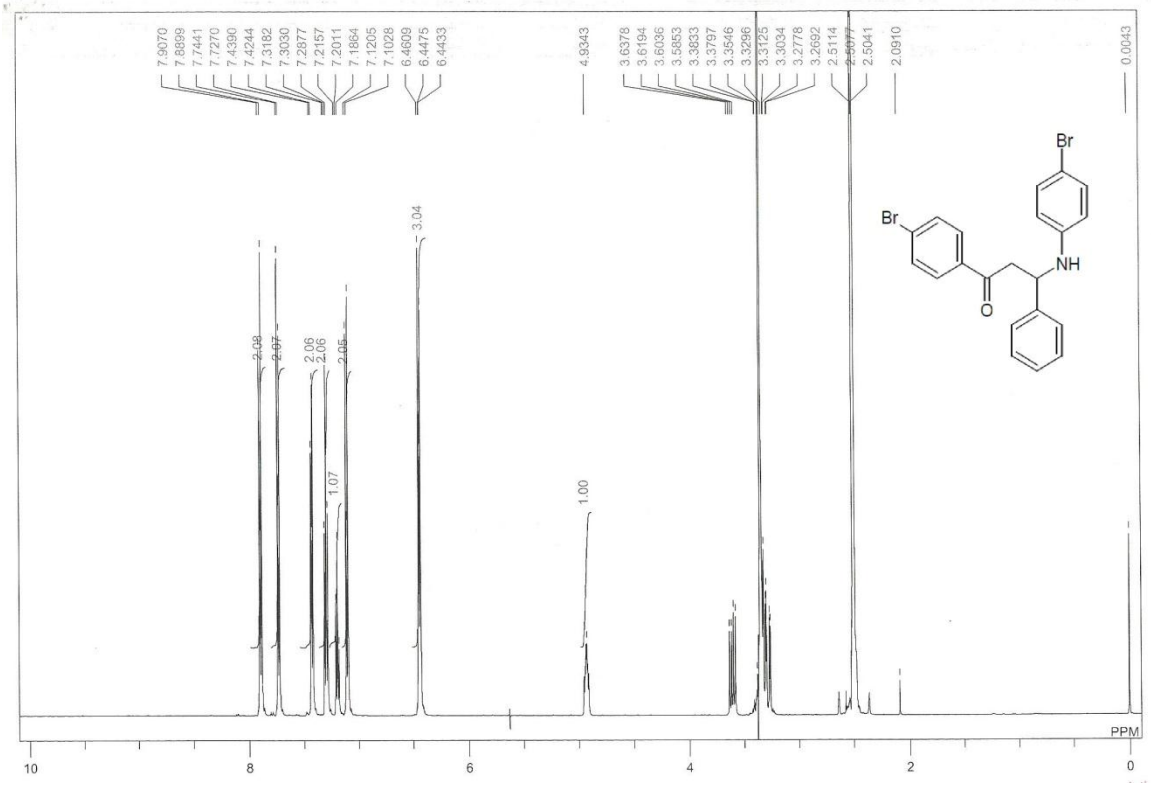


Figure (A.14) ^{1}HNMR spectrum of the Mannich base (VII)

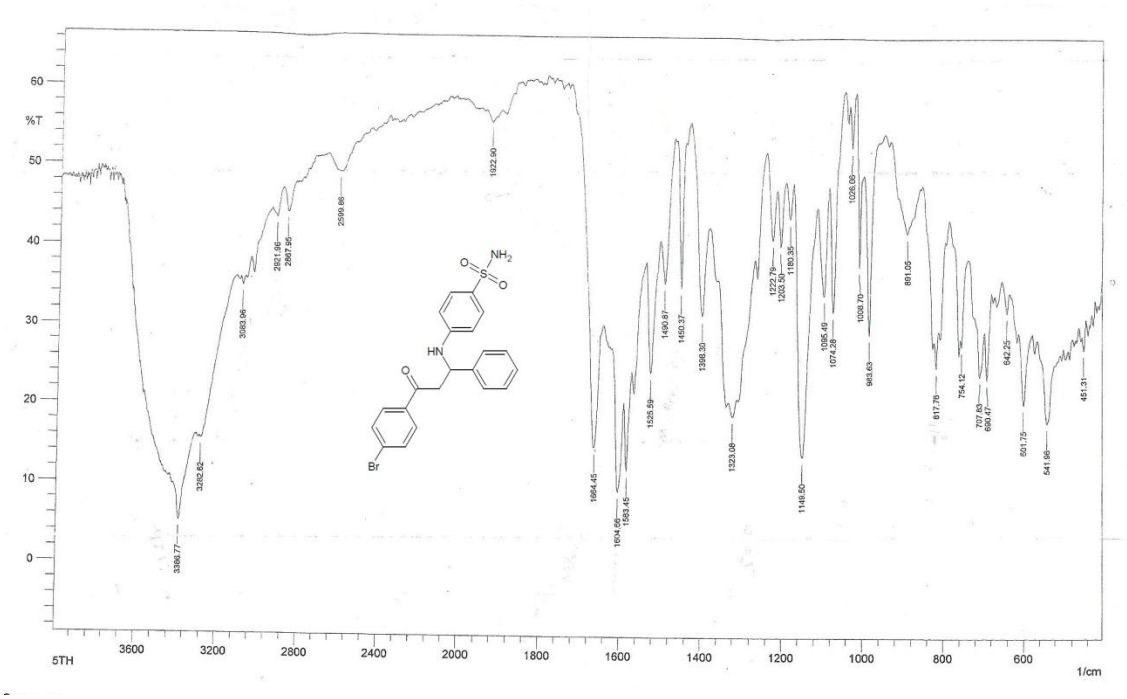


Figure (A.15) IR spectrum of the Mannich base (VIII)

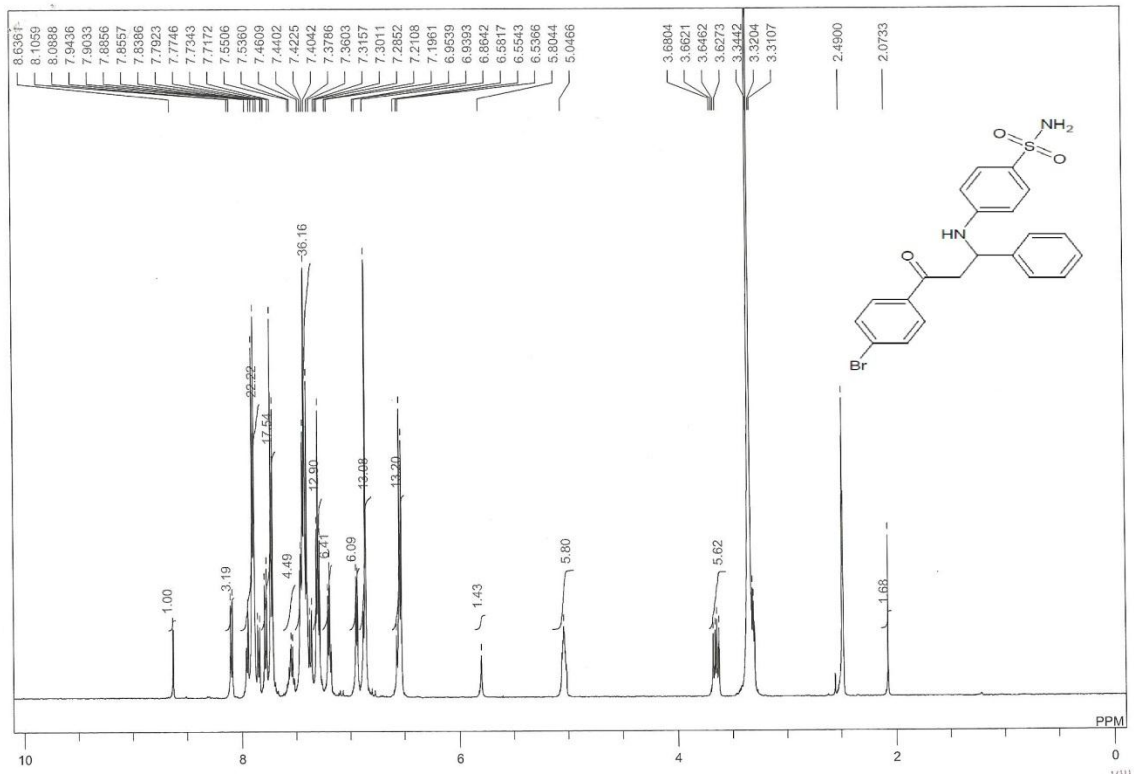


Figure (A.16) ^{1}HNMR spectrum of the Mannich base (VIII)

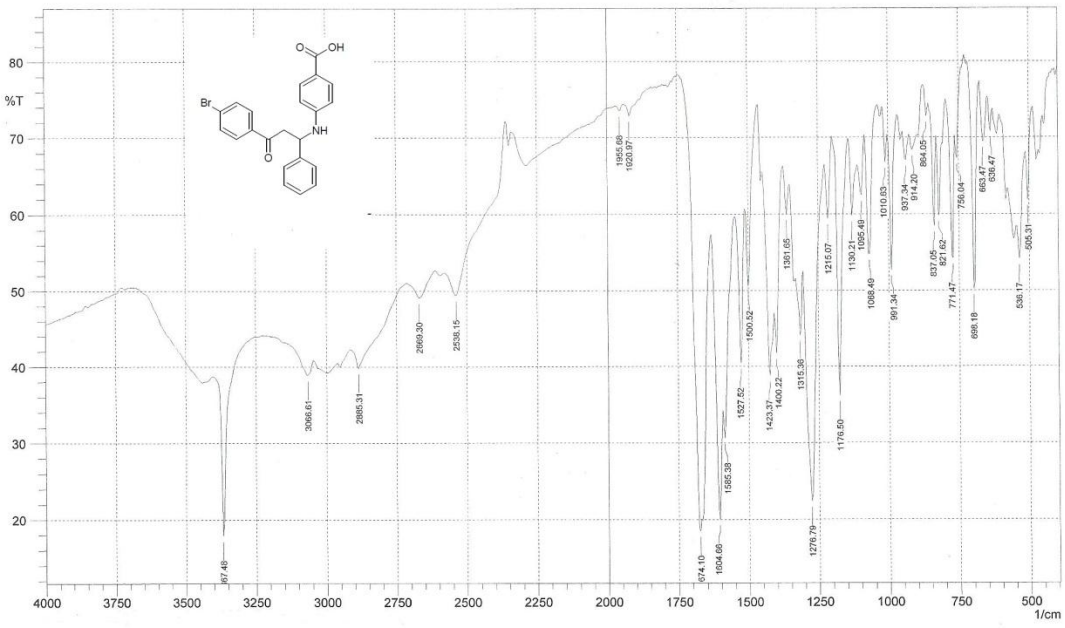


Figure (A.17) IR spectrum of the Mannich base (IX)

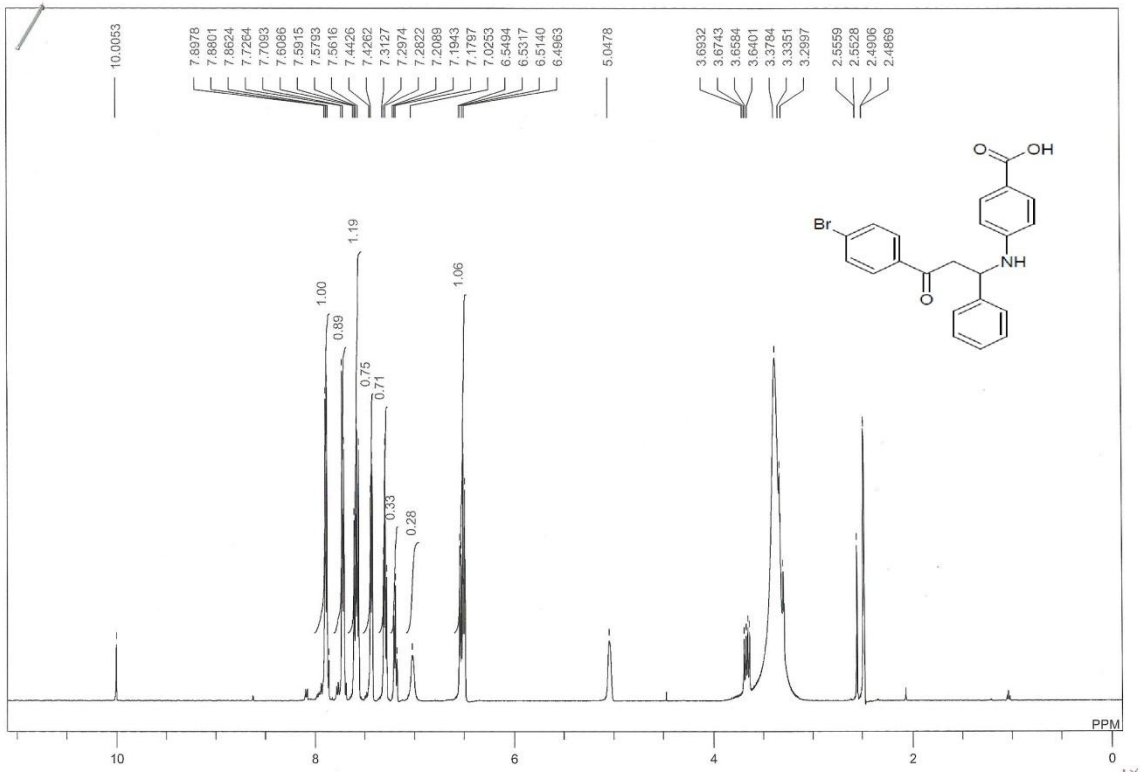


Figure (A.18) ^{1}HNMR spectrum of the Mannich base (IX)

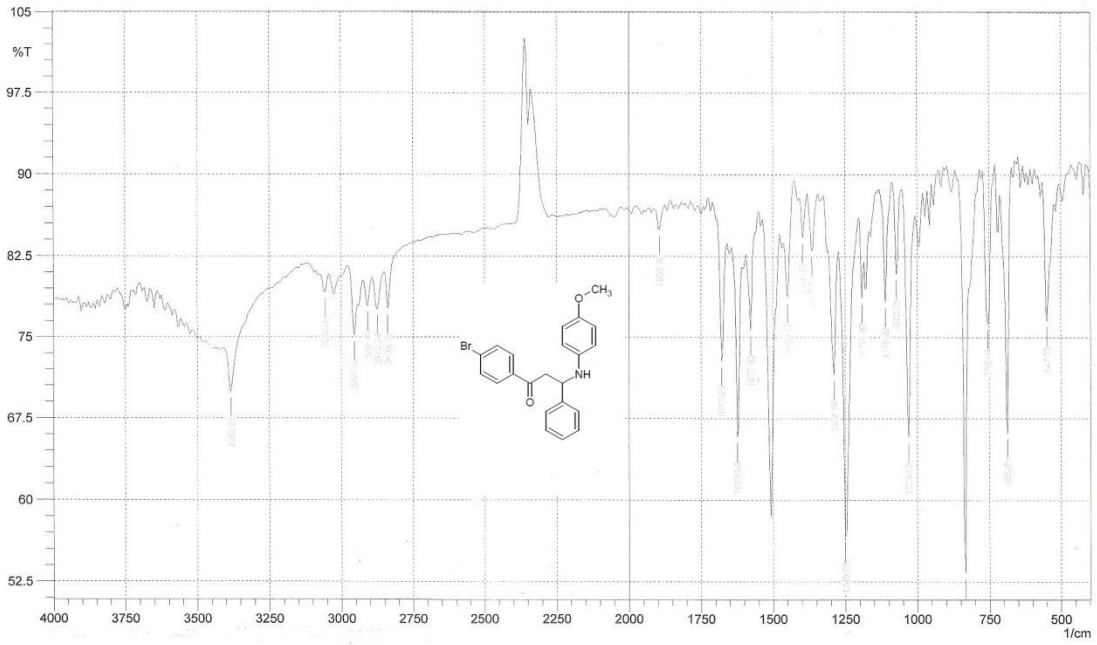


Figure (A.2) IR spectrum of the Mannich base (X)

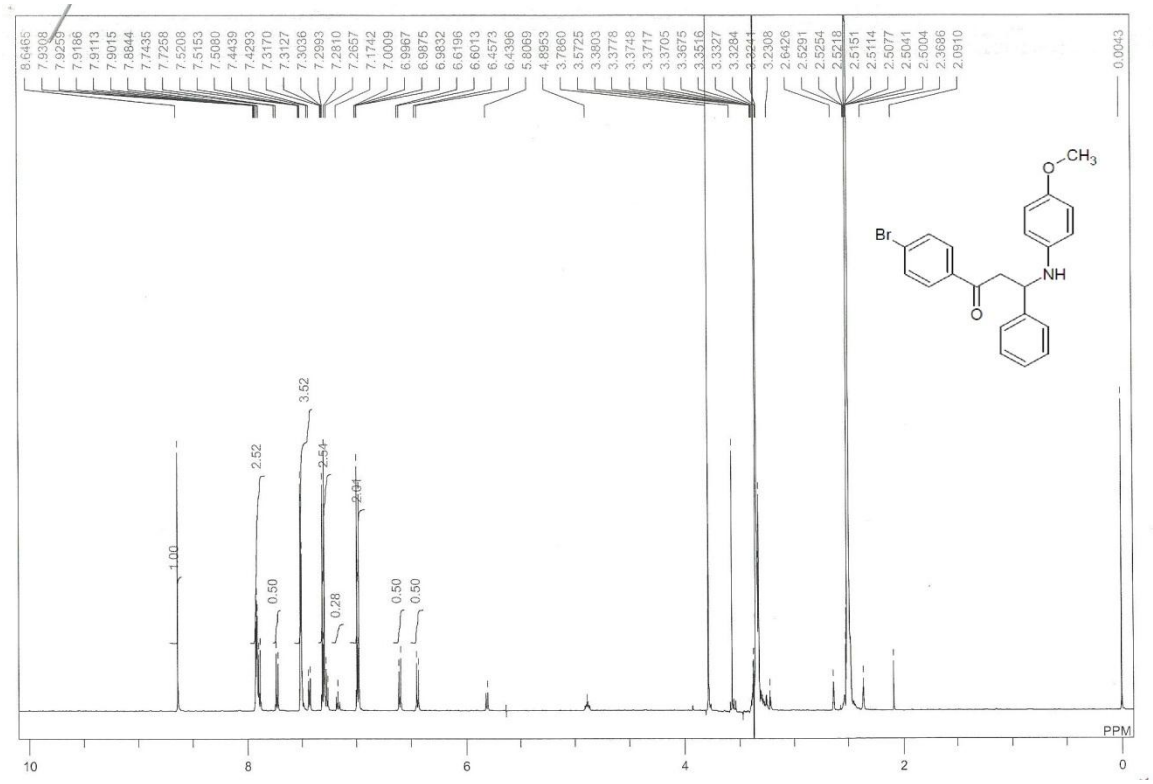
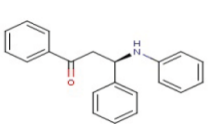


Figure (A.20) ^{1}HNMR spectrum of the Mannich base (X)

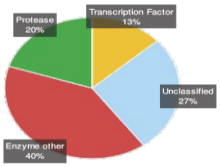
Swiss target prediction reports

Reference:
Gfeller D., Michielin O. & Zoete V.
Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

Query Molecule



Frequency of Target Class

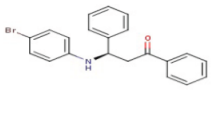


Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Progesterone receptor	P06401	PGR	CHEMBL208		245 / 49	Transcription Factor
Androgen receptor	P10275	AR	CHEMBL1871		100 / 50	Transcription Factor
Muscleblind-like protein 1	Q9NR56	MBNL1	CHEMBL1293317		1044 / 67	Unclassified
Muscleblind-like protein 2 *(by homology)*	Q5VZF2	MBNL2			1044 / 67	Unclassified
Muscleblind-like protein 3 *(by homology)*	Q9NUK0	MBNL3			1044 / 67	Unclassified
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		1177 / 90	Unclassified
Histone deacetylase 3 *(by homology)*	O15379	HDAC3	CHEMBL1829		29 / 82	Enzyme
Histone deacetylase 1	Q13547	HDAC1	CHEMBL325		29 / 82	Enzyme
Histone deacetylase 2 *(by homology)*	Q92769	HDAC2	CHEMBL1937		29 / 82	Enzyme
FAD-linked sulfhydryl oxidase ALR	P55789	GFER	CHEMBL1741189		178 / 31	Enzyme
Neutrophil elastase	P08246	ELANE	CHEMBL248		72 / 7	Serine Protease
Azurocidin *(by homology)*	P20160	AZU1			72 / 7	Serine Protease
Myeloblastin *(by homology)*	P24158	PRTN3	CHEMBL3900		72 / 7	Serine Protease
Arachidonate 5-lipoxygenase	P09917	ALOX5	CHEMBL215		59 / 13	Enzyme
Arachidonate 15-lipoxygenase	P16050	ALOX15	CHEMBL2903		55 / 13	Enzyme

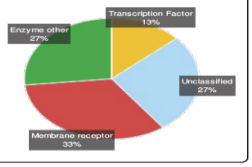
Figure (A.21) Swiss target prediction report of the Mannich base (I)

Reference:
Gfeller D., Michielin O. & Zoete V.
Shaping the interaction landscape of bioactive molecules, *Bioinformatics* (2013) 29:3073-3079.

Query Molecule

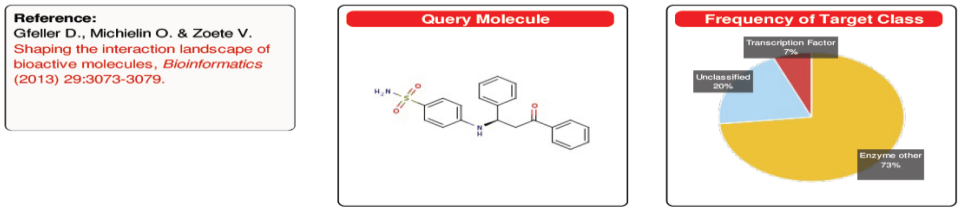


Frequency of Target Class



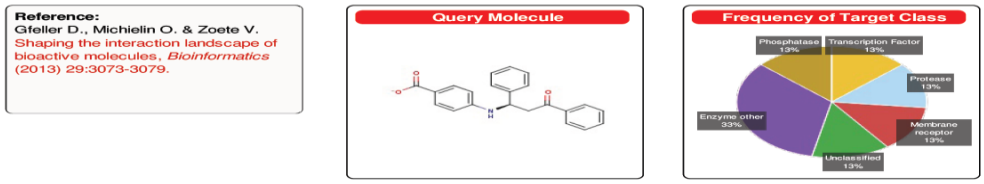
Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Progesterone receptor	P06401	PGR	CHEMBL208		239 / 46	Transcription Factor
Androgen receptor	P10275	AR	CHEMBL1871		102 / 45	Transcription Factor
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		1290 / 75	Unclassified
Muscleblind-like protein 1	Q9NR56	MBNL1	CHEMBL1293317		1131 / 49	Unclassified
Muscleblind-like protein 2 *(by homology)*	Q5VZF2	MBNL2			1131 / 49	Unclassified
Muscleblind-like protein 3 *(by homology)*	Q9NUK0	MBNL3			1131 / 49	Unclassified
C-C chemokine receptor type 1	P32246	CCR1	CHEMBL2413		78 / 38	Membrane receptor
C-C chemokine receptor type 2 *(by homology)*	P41597	CCR2	CHEMBL4015		78 / 39	Membrane receptor
C-C chemokine receptor type 3 *(by homology)*	P51677	CCR3	CHEMBL3473		78 / 38	Membrane receptor
C-C chemokine receptor type 5	P51681	CCR5	CHEMBL274		78 / 39	Membrane receptor
C-C chemokine receptor-like 2 *(by homology)*	C9JP23	CCRL2			75 / 35	Membrane receptor
FAD-linked sulfhydryl oxidase ALR	P55789	GFER	CHEMBL1741189		203 / 17	Enzyme
Arachidonate 5-lipoxygenase	P09917	ALOX5	CHEMBL215		57 / 12	Enzyme
Arachidonate 15-lipoxygenase	P16050	ALOX15	CHEMBL2903		54 / 12	Enzyme
Arachidonate 12-lipoxygenase, 12S-type *(by homology)*	P18054	ALOX12	CHEMBL3687		54 / 12	Enzyme

Figure (A.22) Swiss target prediction report of the Mannich base (II)



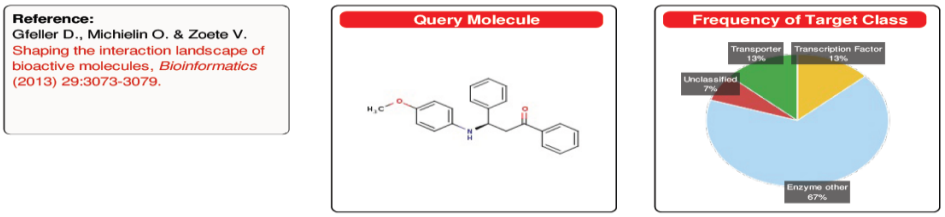
Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Carbonic anhydrase 1	P00915	CA1	CHEMBL261		647 / 220	Enzyme
Carbonic anhydrase 2	P00918	CA2	CHEMBL205		647 / 220	Enzyme
Carbonic anhydrase 3 *(by homology)*	P07451	CA3	CHEMBL2885		647 / 220	Enzyme
Carbonic anhydrase 5A, mitochondrial *(by homology)*	P35218	CA5A	CHEMBL4789		647 / 220	Enzyme
Carbonic anhydrase 7 *(by homology)*	P43166	CA7	CHEMBL2326		647 / 220	Enzyme
Carbonic anhydrase 9	Q16790	CA9	CHEMBL3594		317 / 89	Enzyme
Carbonic anhydrase 13 *(by homology)*	Q8N1Q1	CA13	CHEMBL3912		647 / 220	Enzyme
Carbonic anhydrase 5B, mitochondrial *(by homology)*	Q9Y2D0	CA5B	CHEMBL3969		647 / 220	Enzyme
Muscleblind-like protein 1	Q9NR56	MBNL1	CHEMBL1293317		1537 / 50	Unclassified
Muscleblind-like protein 2 *(by homology)*	Q5VZF2	MBNL2			1537 / 50	Unclassified
Muscleblind-like protein 3 *(by homology)*	Q9NUK0	MBNL3			1537 / 50	Unclassified
Carbonic anhydrase 4 *(by homology)*	P22748	CA4	CHEMBL3729		236 / 99	Enzyme
Carbonic anhydrase 12	O43570	CA12	CHEMBL3242		213 / 56	Enzyme
Carbonic anhydrase 14	Q9ULX7	CA14	CHEMBL3510		213 / 56	Enzyme
Progesterone receptor	P06401	PGR	CHEMBL208		120 / 45	Transcription Factor

Figure (A.23) Swiss target prediction report of the Mannich base (III)



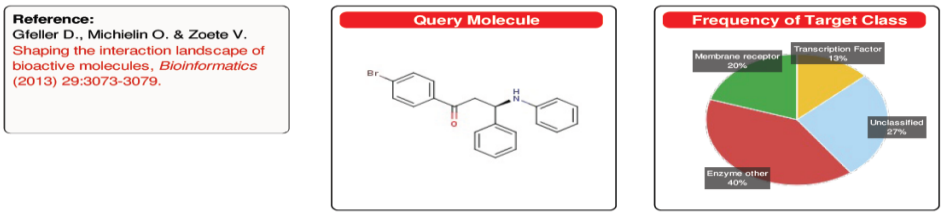
Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Androgen receptor	P10275	AR	CHEMBL1871		3 / 47	Transcription Factor
Progesterone receptor	P06401	PGR	CHEMBL208		2 / 68	Transcription Factor
Neprilysin	P08473	MME	CHEMBL1944		382 / 9	Metallo Protease
Membrane metallo-endopeptidase-like 1, soluble form *(by homology)*	Q495T6	MMEL1			382 / 9	Metallo Protease
Hydroxycarboxylic acid receptor 2	Q8TDS4	HCAR2	CHEMBL3785		29 / 19	Membrane receptor
Hydroxycarboxylic acid receptor 3 *(by homology)*	P49019	HCAR3	CHEMBL4421		29 / 19	Membrane receptor
Hydroxycarboxylic acid receptor 1 *(by homology)*	Q9BXC0	HCAR1	CHEMBL1075101		29 / 19	Unclassified
Arachidonate 5-lipoxygenase	P09917	ALOX5	CHEMBL215		53 / 12	Enzyme
Arachidonate 15-lipoxygenase	P16050	ALOX15	CHEMBL2903		53 / 12	Enzyme
Arachidonate 12-lipoxygenase, 12S-type *(by homology)*	P18054	ALOX12	CHEMBL3687		53 / 12	Enzyme
Arachidonate 15-lipoxygenase B *(by homology)*	O15296	ALOX15B	CHEMBL2457		53 / 12	Enzyme
Epidermis-type lipoxygenase 3 *(by homology)*	Q9BYJ1	ALOXE3			53 / 12	Enzyme
Tyrosine-protein phosphatase non-receptor type 2 *(by homology)*	P17706	PTPN2	CHEMBL3807		65 / 8	Tyr Phosphatase
Tyrosine-protein phosphatase non-receptor type 1	P18031	PTPN1	CHEMBL335		65 / 8	Tyr Phosphatase
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		132 / 90	Unclassified

Figure (A.24) Swiss target prediction report of the Mannich base (IV)



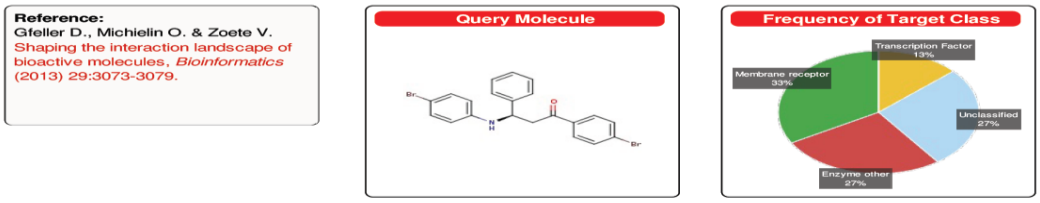
Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Progesterone receptor	P06401	PGR	CHEMBL208		227 / 58	Transcription Factor
Androgen receptor	P10275	AR	CHEMBL1871		112 / 54	Transcription Factor
Histone deacetylase 3 *(by homology)*	O15379	HDAC3	CHEMBL1829		235 / 89	Enzyme
Histone deacetylase 1	Q13547	HDAC1	CHEMBL325		235 / 89	Enzyme
Histone deacetylase 2	Q92769	HDAC2	CHEMBL1937		235 / 89	Enzyme
Cholinesterase	P06276	BCHE	CHEMBL1914		194 / 195	Enzyme
Acetylcholinesterase	P22303	ACHE	CHEMBL220		194 / 195	Enzyme
Arachidonate 5-lipoxygenase	P09917	ALOX5	CHEMBL215		95 / 18	Enzyme
Arachidonate 15-lipoxygenase	P16050	ALOX15	CHEMBL2903		94 / 18	Enzyme
Arachidonate 12-lipoxygenase, 12S-type *(by homology)*	P18054	ALOX12	CHEMBL3687		94 / 18	Enzyme
Arachidonate 15-lipoxygenase B *(by homology)*	O15296	ALOX15B	CHEMBL2457		94 / 18	Enzyme
Epidermis-type lipoxygenase 3 *(by homology)*	Q9BYJ1	ALOXE3			94 / 18	Enzyme
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		3266 / 188	Unclassified
Sodium- and chloride-dependent glycine transporter 1	P48067	SLC6A9	CHEMBL2337		151 / 101	Transporter
Sodium- and chloride-dependent glycine transporter 2	Q9Y345	SLC6A5	CHEMBL3060		149 / 101	Transporter

Figure (A.25) Swiss target prediction report of the Mannich base (V)



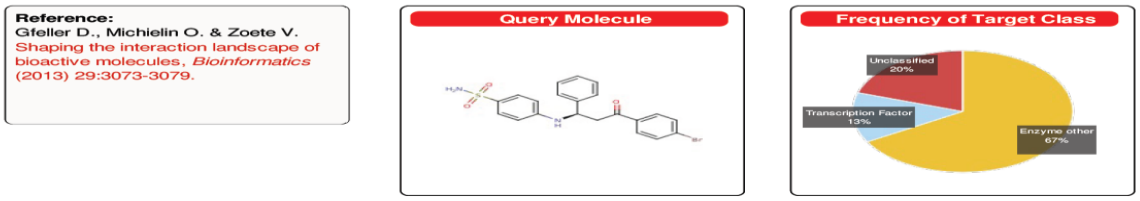
Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Progesterone receptor	P06401	PGR	CHEMBL208		257 / 46	Transcription Factor
Androgen receptor	P10275	AR	CHEMBL1871		110 / 45	Transcription Factor
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		1394 / 77	Unclassified
Muscleblind-like protein 1	Q9NR56	MBNL1	CHEMBL1293317		1194 / 44	Unclassified
Muscleblind-like protein 2 *(by homology)*	Q5VZF2	MBNL2			1194 / 44	Unclassified
Muscleblind-like protein 3 *(by homology)*	Q9NUK0	MBNL3			1194 / 44	Unclassified
Histone deacetylase 3 *(by homology)*	O15379	HDAC3	CHEMBL1829		45 / 55	Enzyme
Histone deacetylase 1	Q13547	HDAC1	CHEMBL325		45 / 55	Enzyme
Histone deacetylase 2	Q92769	HDAC2	CHEMBL1937		45 / 55	Enzyme
Cannabinoid receptor 1	P21554	CNR1	CHEMBL218		1071 / 36	Membrane receptor
Cannabinoid receptor 2	P34972	CNR2	CHEMBL253		733 / 34	Membrane receptor
FAD-linked sulfhydryl oxidase ALR	P55789	GFER	CHEMBL1741189		204 / 16	Enzyme
Cholinesterase *(by homology)*	P06276	BCHE	CHEMBL1914		102 / 89	Enzyme
Acetylcholinesterase	P22303	ACHE	CHEMBL220		102 / 89	Enzyme
C-C chemokine receptor type 1	P32246	CCR1	CHEMBL2413		97 / 36	Membrane receptor

Figure (A.26) Swiss target prediction report of the Mannich base (VI)



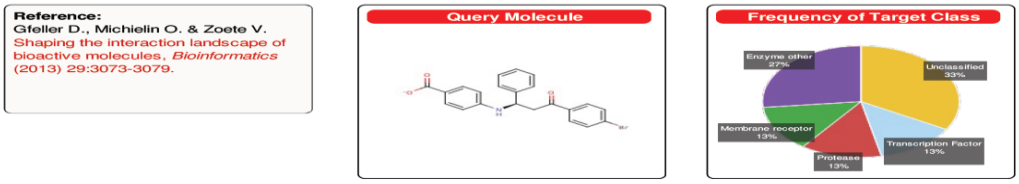
Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Progesterone receptor	P06401	PGR	CHEMBL208		210 / 46	Transcription Factor
Androgen receptor	P10275	AR	CHEMBL1871		92 / 44	Transcription Factor
Muscleblind-like protein 1	Q9NR56	MBNL1	CHEMBL1293317		1185 / 42	Unclassified
Muscleblind-like protein 2 *(by homology)*	Q5VZF2	MBNL2			1185 / 42	Unclassified
Muscleblind-like protein 3 *(by homology)*	Q9NUK0	MBNL3			1185 / 42	Unclassified
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		1301 / 70	Unclassified
Histone deacetylase 3 *(by homology)*	O15379	HDAC3	CHEMBL1829		48 / 45	Enzyme
Histone deacetylase 1	Q13547	HDAC1	CHEMBL325		48 / 45	Enzyme
Histone deacetylase 2 *(by homology)*	Q92769	HDAC2	CHEMBL1937		48 / 45	Enzyme
C-C chemokine receptor type 1	P32246	CCR1	CHEMBL2413		86 / 27	Membrane receptor
C-C chemokine receptor type 2 *(by homology)*	P41597	CCR2	CHEMBL4015		86 / 28	Membrane receptor
C-C chemokine receptor type 3 *(by homology)*	P51677	CCR3	CHEMBL3473		86 / 27	Membrane receptor
C-C chemokine receptor type 5	P51681	CCR5	CHEMBL274		86 / 28	Membrane receptor
C-C chemokine receptor-like 2 *(by homology)*	C9JP23	CCRL2			82 / 25	Membrane receptor
Arachidonate 5-lipoxygenase	P09917	ALOX5	CHEMBL215		51 / 12	Enzyme

Figure (A.27) Swiss target prediction report of the Mannich base (VII)



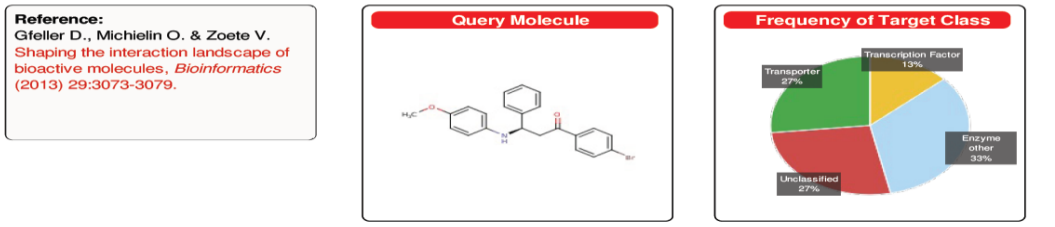
Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Carbonic anhydrase 1	P00915	CA1	CHEMBL261		450 / 139	Enzyme
Carbonic anhydrase 2	P00918	CA2	CHEMBL205		450 / 139	Enzyme
Carbonic anhydrase 3 *(by homology)*	P07451	CA3	CHEMBL2885		450 / 139	Enzyme
Carbonic anhydrase 5A, mitochondrial *(by homology)*	P35218	CA5A	CHEMBL4789		450 / 139	Enzyme
Carbonic anhydrase 7 *(by homology)*	P43166	CA7	CHEMBL2326		450 / 139	Enzyme
Carbonic anhydrase 9	Q16790	CA9	CHEMBL3594		201 / 69	Enzyme
Carbonic anhydrase 13 *(by homology)*	Q8N1Q1	CA13	CHEMBL3912		450 / 139	Enzyme
Carbonic anhydrase 5B, mitochondrial *(by homology)*	Q9Y2D0	CA5B	CHEMBL3969		450 / 139	Enzyme
Progesterone receptor	P06401	PGR	CHEMBL208		93 / 43	Transcription Factor
Muscleblind-like protein 1	Q9NR56	MBNL1	CHEMBL1293317		814 / 31	Unclassified
Muscleblind-like protein 2 *(by homology)*	Q5VZF2	MBNL2			814 / 31	Unclassified
Muscleblind-like protein 3 *(by homology)*	Q9NUK0	MBNL3			814 / 31	Unclassified
Androgen receptor	P10275	AR	CHEMBL1871		70 / 38	Transcription Factor
Carbonic anhydrase 12	O43570	CA12	CHEMBL3242		148 / 42	Enzyme
Carbonic anhydrase 14	Q9ULX7	CA14	CHEMBL3510		148 / 42	Enzyme

Figure (A.28) Swiss target prediction report of the Mannich base (VIII)



Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Muscleblind-like protein 1	Q9NR56	MBNL1	CHEMBL1293317		98 / 34	Unclassified
Muscleblind-like protein 2 *(by homology)*	Q5VZF2	MBNL2			98 / 34	Unclassified
Muscleblind-like protein 3 *(by homology)*	Q9NUK0	MBNL3			98 / 34	Unclassified
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		138 / 67	Unclassified
Progesterone receptor	P06401	PGR	CHEMBL208		2 / 63	Transcription Factor
Neprilysin	P08473	MME	CHEMBL1944		390 / 7	Metallo Protease
Membrane metallo-endopeptidase-like 1, soluble form *(by homology)*	Q495T6	MMEL1			390 / 7	Metallo Protease
Androgen receptor	P10275	AR	CHEMBL1871		3 / 42	Transcription Factor
Hydroxycarboxylic acid receptor 2	Q8TDS4	HCAR2	CHEMBL3785		29 / 18	Membrane receptor
Hydroxycarboxylic acid receptor 3 *(by homology)*	P49019	HCAR3	CHEMBL4421		29 / 18	Membrane receptor
Hydroxycarboxylic acid receptor 1 *(by homology)*	Q9BXC0	HCAR1	CHEMBL1075101		29 / 18	Unclassified
Arachidonate 5-lipoxygenase	P09917	ALOX5	CHEMBL215		49 / 11	Enzyme
Arachidonate 15-lipoxygenase	P16050	ALOX15	CHEMBL2903		49 / 11	Enzyme
Arachidonate 12-lipoxygenase, 12S-type *(by homology)*	P18054	ALOX12	CHEMBL3687		49 / 11	Enzyme
Arachidonate 15-lipoxygenase B *(by homology)*	O15296	ALOX15B	CHEMBL2457		49 / 11	Enzyme

Figure (A.29) Swiss target prediction report of the Mannich base (IX)



Target	Uniprot ID	Gene code	ChEMBL ID	Probability	# sim. cmpds (3D / 2D)	Target Class
Progesterone receptor	P06401	PGR	CHEMBL208		172 / 48	Transcription Factor
Androgen receptor	P10275	AR	CHEMBL1871		89 / 44	Transcription Factor
Histone deacetylase 3 *(by homology)*	O15379	HDAC3	CHEMBL1829		225 / 76	Enzyme
Histone deacetylase 1	Q13547	HDAC1	CHEMBL325		225 / 76	Enzyme
Histone deacetylase 2	Q92769	HDAC2	CHEMBL1937		225 / 76	Enzyme
Microtubule-associated protein tau	P10636	MAPT	CHEMBL1293224		2725 / 145	Unclassified
Cholinesterase	P06276	BCHE	CHEMBL1914		122 / 150	Enzyme
Acetylcholinesterase	P22303	ACHE	CHEMBL220		122 / 150	Enzyme
Muscleblind-like protein 1	Q9NR56	MBNL1	CHEMBL1293317		1583 / 84	Unclassified
Muscleblind-like protein 2 *(by homology)*	Q5VZF2	MBNL2			1583 / 84	Unclassified
Muscleblind-like protein 3 *(by homology)*	Q9NUK0	MBNL3			1583 / 84	Unclassified
Sodium- and chloride-dependent glycine transporter 1	P48067	SLC6A9	CHEMBL2337		133 / 88	Transporter
Sodium- and chloride-dependent glycine transporter 2 *(by homology)*	Q9Y345	SLC6A5	CHEMBL3060		131 / 88	Transporter
Sodium-dependent proline transporter *(by homology)*	Q99884	SLC6A7			131 / 88	Transporter
Sodium- and chloride-dependent neutral and basic amino acid transporter B(0+) *(by homology)*	Q9UN76	SLC6A14			131 / 88	Transporter

Figure (A.30) Swiss target prediction report of the Mannich base (X)