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Synthesis of 1-Benzyl-1,2,3,4-Tetrahydroisoquinoline, Part I: Grignard Synthesis of 1-(Substitutedbenzyl)-1,2,3,4-Tetrahydroisoquinoline Models with Potential Antibacterial Activity

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ABSTRACT

Benzyl tetrahydroisoquinoline alkaloids have interesting biological activity. This work aims at investigating Grignard conditions for the preparation of models of 1-(substitutedbenzyl)-1,2,3,4-tetrahydroisoquinoline and to investigate their biological activity. The head 3,4-dihydroisoquinoline **(3a)** was coupled to selected substituted benzyl chloride tails **(4a-g)** at carbon 1 of the tetrahydroisoquinoline unit, utilizing different Grignard conditions. Thorough investigation proved that the best conditions were to stir a mixture of magnesium turnings, iodine crystals, few drops of 1,2-dibromo ethane in THF and the substituted benzyl chloride tail at –10°C, followed by adding **3a** in THF at –80°C. These conditions worked successfully for the preparation of benzyl-tetrahydroisoquinolines **5a-d** with acceptable yields (62-86%). The substituted tails benzyloxybenzyl chloride **4f** and 4-hydroxybenzyl chloride **4e** were added under the same conditions but lower temperatures, furnishing benzyl tetrahydroisoquinolines **5e** and **5f** in low yields (< 8%). An alternative strategy based on lithiation of *N*-benzoyl-1,2,3,4-tetrahydroisoquinoline **13** followed by alkylation of the selected tails produced **5e** and **5f** with satisfactory yields upon hydrolysis of **16**; **5e** (82%) and **5f** (60%). All products and intermediates were isolated, purified and their structure confirmed using NMR, IR and MS techniques. The antibacterial activity against tetracycline resistant MRSA revealed that some compounds were identified as being of potential interest. In particular, compounds **9** (42%), **5e** (82%) and **16** (71%) showed interesting antibacterial activity with MIC ranges of 10 to 64 μg/ml. In conclusion, this research was successful in preparing 1-substituted benzyl models of the tetrahydroisoquinoline nucleus. Such models can be good candidates for further biological activity screening tests.

Keywords: Tetrahydroisoquinolines, Benzyl tetrahydroisoquinolines, Grignard reaction, Antibacterial properties, MRSA.

INTRODUCTION

Isoquinolines are very large group of plant secondary metabolites known as isoquinoline alkaloids, nearly all of which are 1,2,3,4-tetrahydroisoquinoline derivatives. This family of alkaloids have broad spectrum of biological activity. Morphine and emetine, both tetrahydroisoquinoline derivatives, are medicinally valuable members of this group of alkaloids[1,2]. Benzyl substituted tetrahydroisoquinoline (Laudanosine, **1**) is also a derivative of the same family with

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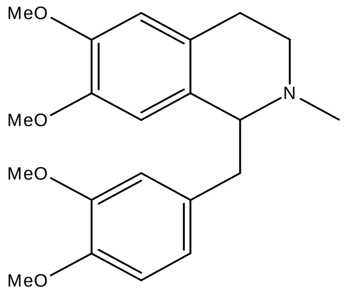
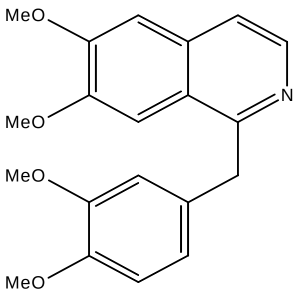
broad activity. Laudanosine **(1)** was reported as potential SK channel blockers[3]. The opium poppy alkaloid papaverine **(2)** is one of the most potent coronary vasodilators[2].

Chart 1



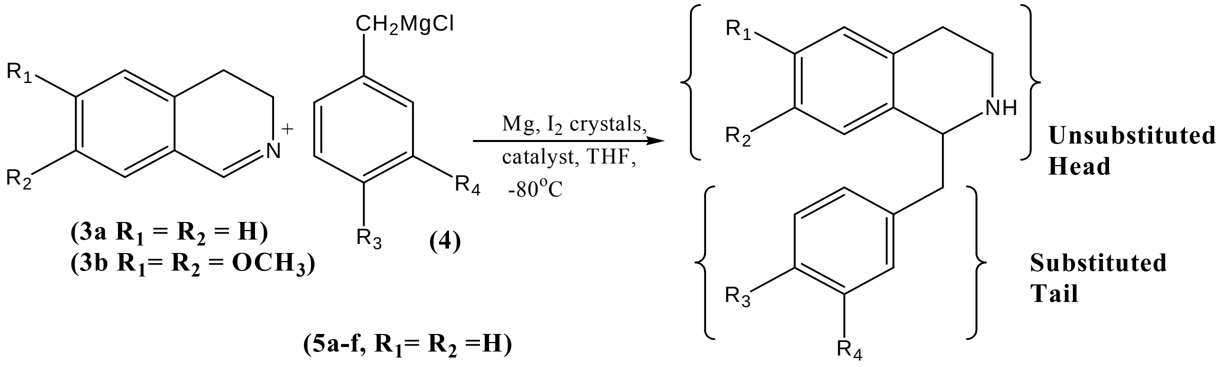
(1) Laudanosine (Tetrahydroisoquinoline)



(2) Papaverine (Isoquinoline)

Such interesting broad spectrum of biological activity and applications have drawn our attention to prepare naturally occurring compounds and/ or derivatives with more potent activity and superior pharmacokinetic profile. However, we have to investigate first the most efficient method using selected models. Therefore, the aim of this work is to prepare stripped-down models of 1-substitutedbenzyl-1,2,3,4- tetrahydroisoquinoline **(5a-f)** with potential activity and to investigate the methods and conditions of the reactions involved. This part deals mainly with Grignard conditions, **(Scheme 1)**.

Scheme 1



(3a $R_1 = R_2 = H$)
(3b $R_1 = R_2 = OCH_3$)

(4)

(5a-f, $R_1 = R_2 = H$)

a- $R_3 = R_4 = H$;
b- $R_3 = CH_3$, $R_4 = H$;
c- $R_3 = OCH_3$, $R_4 = H$
d- $R_3 = R_4 = OCH_3$;
e- $R_3 = OH$, $R_4 = H$
f- $R_3 = OCH_2C_6H_5$, $R_4 = H$;
g- $R_1 = R_2 = R_3 = R_4 = OCH_3$

(5a-f) Target models

Benzyl Tetrahydroisoquinoline nucleous

RESULTS AND DISCUSSION

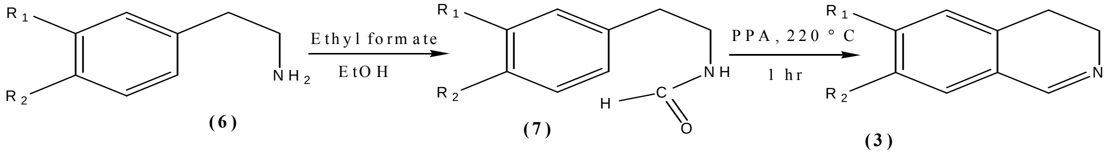
Benzylisoquinolines (BIQs) are naturally occurring alkaloids with a broad spectrum of activity. The diversity in their structure and biological activity captured the attention of many phytochemists and medicinal chemists, either to isolate or to investigate new derivatives. Preparation of these derivatives was reported in the literature utilizing different routes[4-12]. The first general route involved building up the 1-benzyl substituted isoquinoline system. Bischler-Napieralski synthesis usually starts by preparation of the amides by the reaction of phenylethylamine with a carboxylic acid or acid chloride, followed by cyclization of the *N*-formyl derivative with a dehydrating agent such as polyphosphoric acid (PPA), phosphorous pentoxide (P_2O_5), phosphorous oxychloride ($POCl_3$) and phosphorous pentachloride (PCl_5), to give the 3,4-dihydroisoquinoline derivative[4,5,6]. Alternatively, Pictet Spengler cyclization involves formation of the phenethyl imine first by Schiff base reaction, followed by treatment with concentrated mineral acid to form the 1-benzyl tetrahydroisoquinoline[4]. The use of an activating group para to the position of ring closure in both approaches is mostly needed to reduce the formation of structural isomers[7,8,9]. Such requirements reduced the variety of starting material that limited the preparation of many important BIQs.The second routes involve substitution of benzyl group at position 1 of the isoquinoline system. Although the literature provides different interesting methods to prepare benzyl tetrahydroisoquinolines, only few methods do address substitution at position 1 of the tetrahydro or the dihydroisoquinoline system **(1)** [10, 11]. Upon investigating the literature, it was found that only few hits are available regarding the utilization of Grignard reaction to prepare benzyl isoquinoline and most of them were reported many years ago. Not only they report low yields, but also involve difficult procedures. Moreover, most have failed to introduce substituted benzyl tails on position 1 of the isoquinoline system[10,11,12].

Synthesis: Grignard reaction

In view of the fact that substituted isoquinoline systems are expensive and difficult to be prepared, the stripped model (head) 3,4-dihydroisoquinoline **(3a)** was used to investigate the chemistry of this approach, (**Scheme 2**).

The *N*-formyl **7a** was firstly prepared in good yields by reaction of the amine **6a** with excess ethyl formate in hot ethanol. 3,4-Dihydroisoquinoline **(3a)** was prepared from *N*-formyl-(2-aminoethyl)benzene (**7a**) using polyphosphoric acid as a dehydrating agent (**Scheme 2**)[13-16]. The initial trials of the Bischler-Napieralski cyclization proved to be difficult, due to the absence of para activating group to the position of ring closure. Different dehydrating agents were employed including PPA, $POCl_3$ and P_2O_5. MS analysis gave the molecular ion of **3a** (m/z 131) only when polyphosphoric acid (PPA) was used. The conditions were optimized and the reaction gave a very high yield (98%) when the amide **(7a)** was vigorously stirred at 200-240 °C with PPA in a sand bath for one hour exactly. When the time or temperature was increased, the reaction mixture decomposed. If they were decreased, a mixture of the cyclised and the *N*-formyl starting material **7a** were obtained[17]. It is worth mentioning that distillation of the oily product at high temperatures for purification led to the formation of an oily material that solidify at room temperature in a form of white fine powder. Although NMR analysis of the product showed a pure compound, we were not able to interpret the structure. It is deduced that compound **3a** might have been polymerized or dimerized. Following similar procedures, 6,7-dimethoxy-3,4-dihydroisoquinoline (**3b**) was prepared in satisfactory yields.

Scheme 2

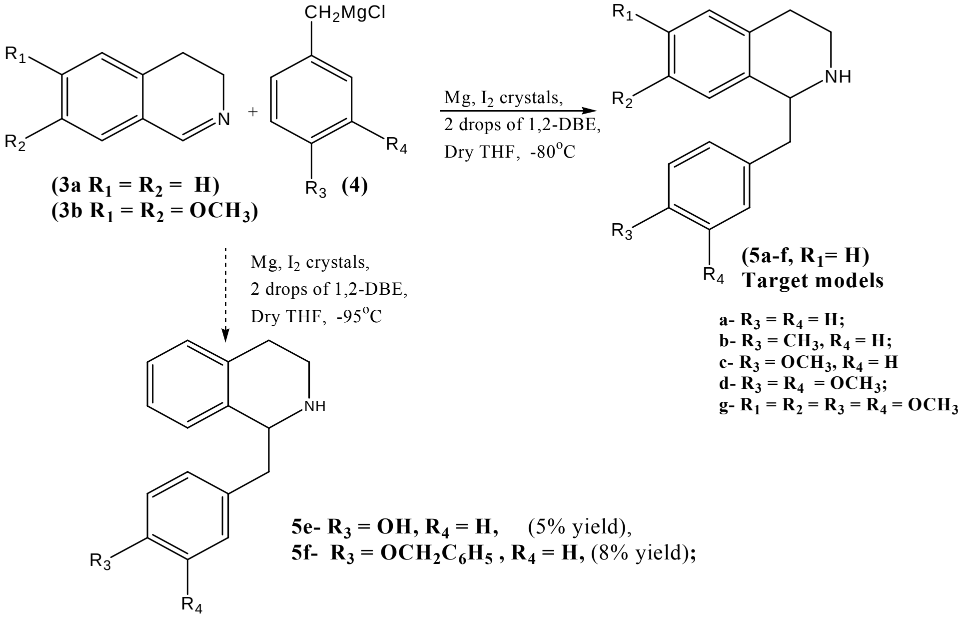


(3)
a - $R_1 = R_2 =$ H)
b - $R_1 = R_2 =$ OCH_3

Using the method reported for the preparation of 1-phenyltetrahydroisoquinoline[12], 1-benzyl-1, 2, 3, 4-tetrahydroisoquinoline **(5a)** was successfully prepared in low yield. Initial conditions involved using dry ether at room temperature, Mg and heating the benzyl chloride at room temperature before adding the isoquinoline head. Employing THF as solvent, Mg turning, 1, 2-dibromo ethane (DBE) and I_2 crystals gave satisfactory yields when the temp was cooled to –10°C. However, employing the same conditions and formation of the Grignard reagent at –10°C followed by cooling at –75 to –80°C before adding the isoqinoline gave best yields and decreased side products, **(Scheme 3)**. With small modifications, the same conditions proved to be efficient in preparing 1-(substitutedbenzyl)-1, 2, 3, 4-tetrahydroisoquinolines **5a-d**. Targets **5e** and **5f** were obtained in very low yields even upon reducing the temperature of coupling to –95°C. Therefore, an alternative strategy was used to prepare both compounds. Oxidation of **5a** and **5f** was observed and will be discussed later.

In order to prove that the substitution on the isoquinoline head would not affect Grignard conditions, the isoquinoline **3b** was coupled with dimethoxy substituted benzyl chloride **4g** using the same conditions. The reaction was successful and furnished 1-(3, 4-dimethoxybenzyl)-6,7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinolines **5g** in reasonable yield, **(Scheme 3)**.

Scheme 3



(3a $R_1 = R_2 =$ H)
(3b $R_1 = R_2 = OCH_3$)

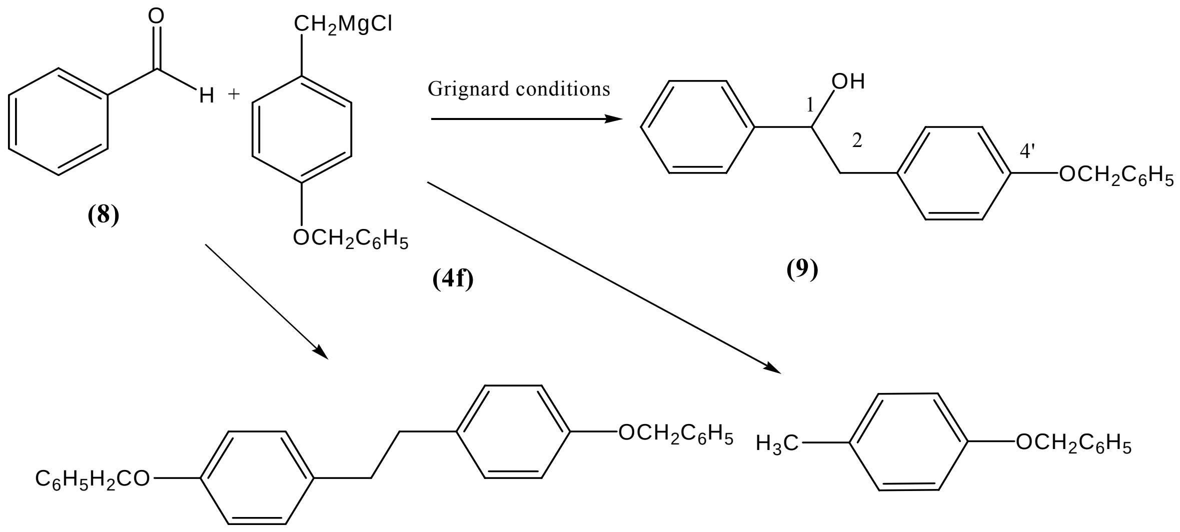
(5a-f, R_1= H)
Target models

a- $R_3 = R_4 = H$;
b- $R_3 = CH_3, R_4 = H$;
c- $R_3 = OCH_3, R_4 = H$
d- $R_3 = R_4 = OCH_3$;
g- $R_1 = R_2 = R_3 = R_4 = OCH_3$

5e- $R_3 = OH, R_4 = H$, (5% yield),
5f- $R_3 = OCH_2C_6H_5$, $R_4 = H$, (8% yield);

To investigate the conditions to prepare **5e** and **5f**, it was decided to investigate reaction conditions of coupling the head **3a** with the 4-benzyloxybenzyl chloride tail, BOBC, using the Grignard reaction to prepare **5f**. All attempts at generating the Grignard reagent using the conditions employed for the preparation of **5a** were unsuccessful for preparing **5f** [11,12]. Only starting materials were obtained and the Grignard reagent did not form. When the tail (BOBC) was added to a mixture of magnesium turnings, an iodine crystal and 2 drops of 1,2-DBE at room temperature[18,19], the Grignard reagent was formed and the reaction produced compound **9** when coupled with benzaldehyde at a very low temperature (-78°C). Two side products were also identified indicating two side reactions occurring at the same time for the tail unit. The two products were the coupled bibenzyl **(10)** and the reduced product **(11)**, **(Scheme 4)**. The initiating temperature was found to be critical to the formation of the reagent. Increasing the temperature led to increased side product formation. Employing same conditions to obtain **5f**, furnished side products **10** and **11** but not **5f**. Decreasing the temperature to –95°C barely produced **5f** and in very low yields. The conditions employed are described in **Table (1)**.

Scheme 4



(10) 1,2-Bis(4'-benzyloxyphenyl)ethane

(11) p-tolylbenzyl ether

NMR analysis showed typical ^{1}H-NMR pattern for almost all targets **5a-g**. The proton of the methyl group appeared upper-field at about 2.0δ, whereas all the peaks of all methoxy groups were desheilded to about 3.8-4.0δ. The methylene protons of C-3, C-4 (CH_2-CH_2-N) and PhCH_2 appeared as 2 multiplets in the range 2.60-3.50δ with total integration equal to 6. The first multiplet appears in the range 2.6 to 3.0 for (CH_2-CH_2-N) and PhCH_2 protons with integration of 4, where as the other multiplet appears in the range of 3.0- 3.5 for C-3 protons CH_2-CH_2-N) deshielded because of the nitrogen. The peaks of the proton of C-1 (N-CH-) appeared as doublet of doublet for all targets around 4.1-4.2δ. ^{13}C-NMR on the other hand was problematic. Although ^{13}C-NMR is not usually needed unless there is a need for further elucidation, ^{13}C-NMR analysis was carried out for many targets. The spectrum was complicated and could not be interpreted clearly for many compounds. For example, ^{13}C-NMR analysis for **5a** was carried out and found that the total number of peaks does exceed the total number of carbons. These results were confirmed based on literature data[12b]. Further search for ^{13}C-NMR literature data of other targets revealed no results. One problem that limited the ^{13}C-NMR analysis is actually the complex NMR data obtained due to conformers in some compounds. Another problem was the low stability of these compounds in solution over the long period of ^{13}C-NMR analysis. The final compounds are stable at RT once they are dried and can be kept for long period of time if dried or in salt form. Once they are in solutions, most should be oxidizing with time (hours). The compounds were stable enough for proton NMR analysis at temperatures not exceeding 100 °C if were analyzed quickly. ^{13}C-NMR analysis needs high number of scans that takes time and have led to oxidation as proved later with compounds **5a** and **5f**. Unfortunately, most were also unstable at higher temperatures that make EA analysis and melting point determination very difficult. Most of these targets were isolated as farley pure semis solids. Further chromatographic techniques led to some oxidation that made their final melting point values not accurate since they oxidize upon further purification. IR analysis proved all expected groups in each compound. Some examples of these peaks are: broad NH stretching in the range of 3300 -3500cm^{-1} , aromatic C-H stretching at about 3050 and 3020, aliphatic C-H stretching at about 2920 and 2800, aromatic C=c stretching at about 1600 and 1486.

Table (1): Conditions employed in preparing the Grignard products from **BOBC (4f)**

BOBC (moles),	**Temp °C**	**Mg turning (moles)**	**SM (1mole)**	**Temp. of addition SM(°C)**	**Initiators**	**Temp °C**	**Stir. time (hrs)**	**Temp (°C)**	**Results***	**Yields**
4	−10	3.85	PhCHO	−78	I_2, 1,2-DBE[#]	R.T	3	−78	No rxn	---
4	−10	3.85	3,4-DHIQ	−78	I_2, 1,2-DBE	R.T	3	−78	No rxn	---
2	R.T.	3.85	PhCHO	R.T.	I_2, 1,2-DBE	35	Overnight	−78	+ve 9 with 10,11	15 % (9), <30% 10,11)
1	0 to −10	3.85	PhCHO	−78	I_2, 1,2-DBE	R.T	Overnight	−78	+ve 9 10 major	42% 50 % (10)
1	−10	3.85	3,4-DHIQ	−78	I_2, 1,2-DBE	R.T	Overnight	−78	No rxn 10,11	--- <40% 10,11)
4	−10	3.85	3,4-DHIQ	−78	I_2, 1,2-DBE	40	Overnight	−78	+ve 10 major, 11	MS Only (5f)
1	−10	3.85	3,4-DHIQ	−95	I_2, 1,2-DBE	R.T	Overnight	−95	+ve 10, 11	8% 5f

* Solvent: THF was used since anhydrous ether gave no results, Dry N_2.

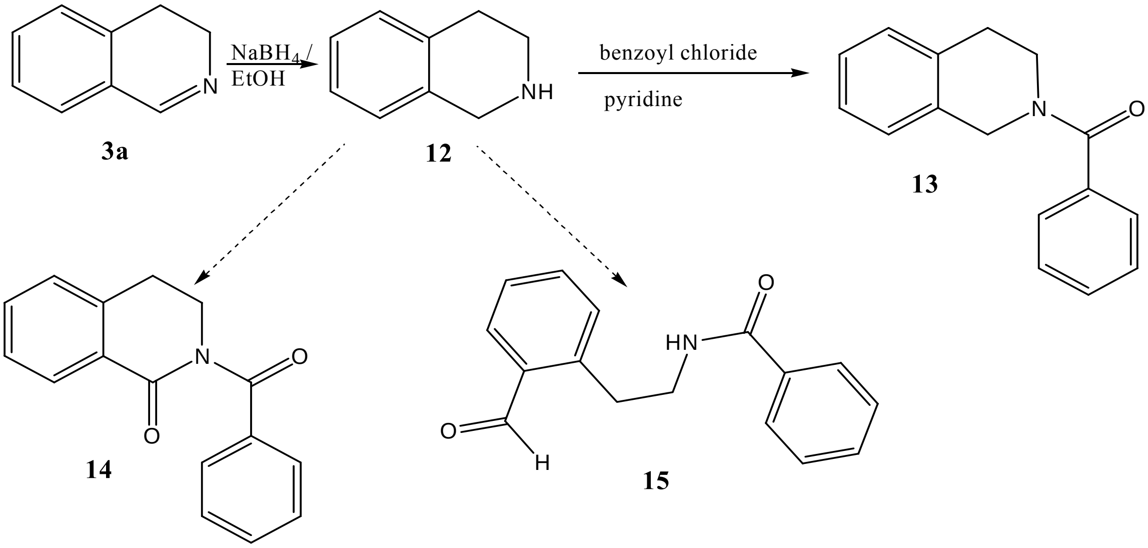
[#] 1,2-DBE: 1,2-dibromo ethane.

Alternative strategy to prepare 5e and 5f: Lithiation / Alkylation strategy

The literature offers a few attractive methods, which introduce substituents in the 1-position of the isoquinoline skeleton[20-23]. Most of these methods are based on reversing the role of each moiety, i.e. using the isoquinoline moiety in a nucleophilic sense and the benzyl chloride as the electrophile species. The nucleophilic activity in the 1-position of tetrahydroisoquinoline **3a** generated by lithiation is possible and favored if C=O is attached to the N atom[21] . The carbonyl acceptor reactivity must be reduced sufficiently to prevent addition of the nucleophilic base. This cleavage might be prevented by steric protection of the carbonyl through adding a phenyl or $C(CH_3)_3$ (for example), to form the benzoyl or the pivaloyl derivative. The *N*-benzoyl tetrahydroisoquinoline was chosen initially in our work because it can be removed easily, **(Scheme 5, 6)**.

The dihydroisoquinoline **3a** was maintained at reflux overnight with sodium borohydride in ethanol. The tetrahydro derivative (**12**) was produced in 89% yield. Treatment of this compound with benzoyl chloride at 0 °C gave the *N*-benzoyl derivative (**13**) as a thick yellow oil (54%). NMR spectrum at room temperature indicated two conformers which coalesced and sharpened at higher temperatures (87°C). NMR of the crude product showed also two oxidised products which were separated by normal phase HPLC. These two oxidised products were identified as compounds **14** (25%) and **15** (10%), (**Scheme 5**).

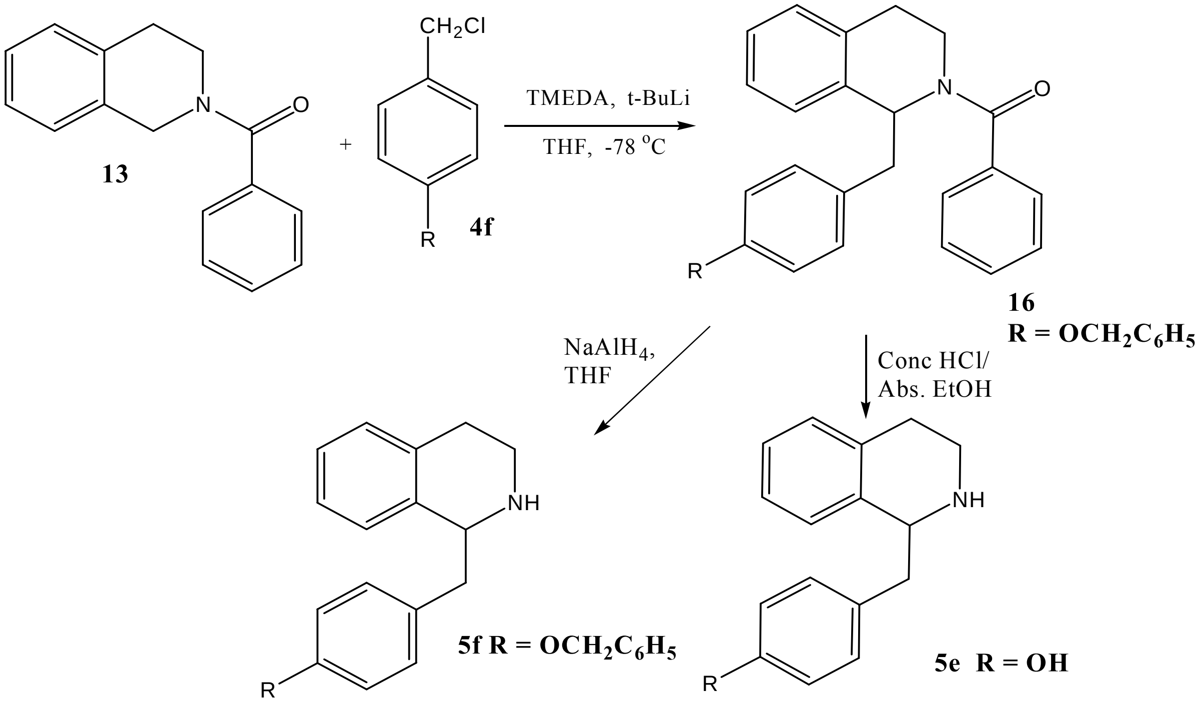
Scheme 5



The initial preparation of compound **16** involved the addition of n-butyl lithium (n-BuLi) and diisopropyl amine (DPA) in THF at −80°C[24] (**Scheme 6**) to the N-benzoyl derivative (**13**). The blue complex formed was stirred for 2 hours at −78°C before adding the electrophile benzyloxybenzyl chloride (**4f**). Unfortunately, although the desired product (**16**) was detected by MS and NMR, the reaction furnished mainly the starting materials and the two oxidized products (**14**) and (**15**). NMR showed minor peaks for the product which was not worth collection for further treatment. MS showed a significant peak for the cleaved product (**5f**) with a molecular ion of m/z (329). This indicated two reactions, one at position 1 and the other at the carbonyl group leading to its cleavage (**Scheme 6**).

Changing the conditions of coupling to tetramethylene ethylenediamine (TMEDA), t-butyl lithium (t-BuLi) in THF[21] and cooling to–78°C before adding benzyloxybenzyl chloride, furnished the desired product 16 with 70 % yield. Although cleavage of the amide was achieved by direct heating of 16 with $NaAlH_4$ in THF, the crude product of 16 was further treated with $NaAlH_4$ or dilute HCl to prepare 5f directly and in good yields. Treating of 16 or 5f directly with conc. HCl in absolute ethanol gave the target 5e, (**Scheme 6**).

Scheme 6

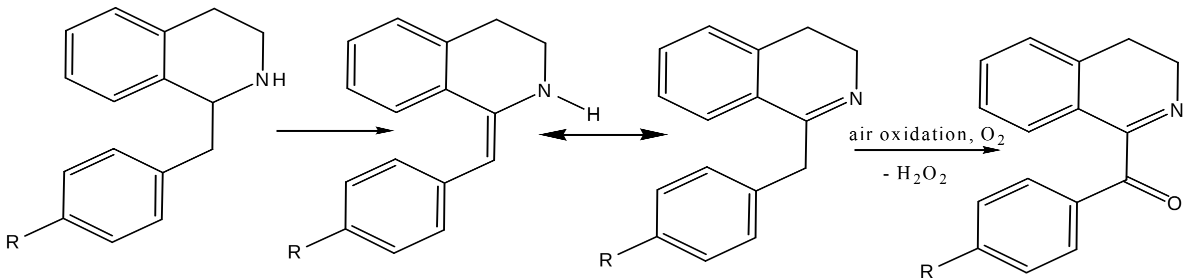


Structural determination of compounds **13** and **16** was difficult since 1H-NMR was not clear. Those two compounds share the amide group that can be represented in two conformers. The N-Benzoyl amide of compound **13**, as an example, showed 2 conformers at room temperature. This effect restricts the rotation of each conformer affecting the peaks of the surrounding atoms. The machine sees each conformer as a different compound and gives different peaks for the affected surrounded atom. For example: the protons of C-1 (Ar-C-$\underline{H}_2$-N) in compound **13** showed two singlet peaks with different intensities and integration at RT although should appear as singlet; the first peak appeared at 4.59 (0.66H, b-s, Ar-CH_2-NH) and the second appeared at 4.91 (1.34H, b-s, Ar-CH_2-NH). The total integration value was 2 and represents the 2 protons of Ar-C$\underline{H}_2$-N. This phenomenon of restriction in rotation around the amide can be reduced and further disappeared if the analysis was carried out at higher temperature (Variable temp analysis). The analysis at 87 ºC showed the same protons as one singlet peak at 4.68δ with integration equal to 2.

Oxidation of compound 5a and 5f to 18a and 18f

1-Benzyl-3,4-dihydroisoquinoline has been reported to oxidize to enamine **17** when exposed to air. The oxidation occurs mainly at the benzylic carbon atom to form the ketone derivative 1-benzoyl-3,4-dihydroisoquinoline (**18a**)[25]**.** Dehydrogenation of the dihydro aromatic ring to form 1-benzoylisoquinoline may accompany ketone formation[26]. The mechanism, which involves the enamine intermediate (**17**) from 1-benzyl-3,4-dihydroisoquinoline, is fully explained in the literature[27,28] (**Scheme 7**).

Scheme 7



5a R = H
5f R = $OCH_2C_6H_5$

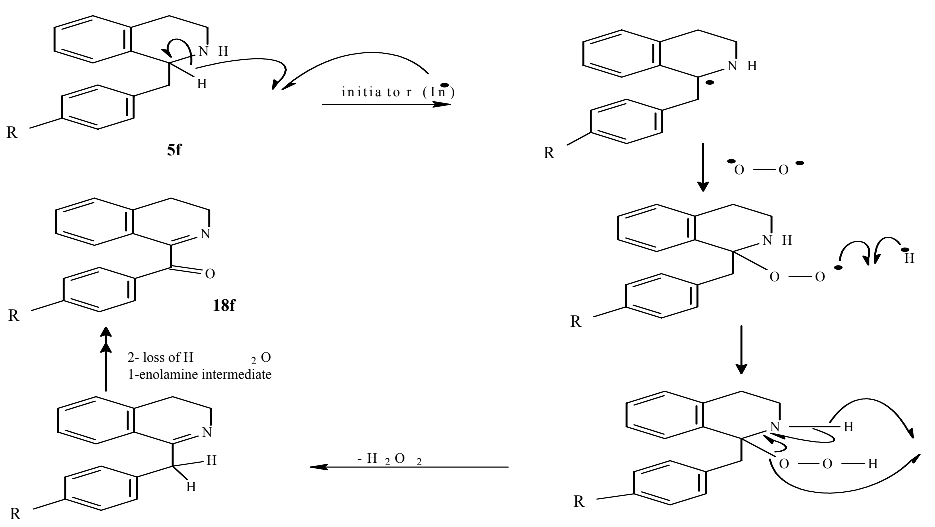
17
Enamine intermediate

17

18
a R = H
f R = $OCH_2C_6H_5$

On the other hand, oxidation of 1-benzyl-1,2,3,4-tetrahydroisoquinolines such as **5a** and **5f** to 1-benzyloxybenzoyl-3,4-dihydroisoquinoline or (4-benzyloxyphenyl) - (3, 4- dihydroisoquinolin- 1-yl) methanone **(18f)** has no precedent in the literature. In the process of purification of the 1-benzyl compound **(5f)**, the compound was found to be unstable in solution and new spots were observed on TLC ($R_f = 0.61$). Oxidation of **5f** was followed by MS analysis. When the product was left exposed to air for a long time, the molecular ion peak of **5f** disappeared and a new peak was observed indicating a molecular ion of m/z 341 for **18f**, **(Scheme 7)**. The NMR and the MS provided clear evidence for the oxidized product, therefore, we propose a mechanism for such oxidation based on the formation of the benzyl dihydro intermediate first through losing a molecule of H_2O_2 **(Scheme 8)**, followed by the formation of the benzoyldihydro derivative as described in **Scheme 8**.

Scheme 8



Biological evaluation

It was recognized that there was no evidence in the literature to suggest that the intermediates produced through out the course of this work would posses a spectrum of antimicrobial activity. In view of the fact that appropriate screens were accessible, it was considered that screening some of the compounds available was opportunistic and worthwhile.

Activity against tetracycline resistant MRSA was evaluated at the Pharmacognosy and Phytotherapy Centre, The School of Pharmacy, University of London. More than 16 compounds (intermediates) were sent for biological evaluation. Only 3 showed positive results and the initial results of those are shown in Table (2).

Table 2: Results of antimicrobial evaluation of the active compounds only

Compound	Antibiotic activity	MIC lowering activity	MIC (μg/ml)
16	No	Yes (MIC lowered by factor 2)	64
5e	No	Yes (MIC lowered by factor 4)	32
9	Yes	>4	10

* Activity evaluated against tetracycline-resistant MRSA,

* The standard used was tetracycline.

In conclusion, despite the fact that the assay is not very selective, the initial evaluation results provided a number of candidates for future biological screening. Although the low activities made it difficult to establish structure activity correlation, some compounds were identified as being of potential interest. Compound **(9)** was found to exhibit antimicrobial activity at 10μg/ml. All the final compounds of benzylisoquinolines and intermediates will be sent for biological evaluation; antibacterial, antiviral and antimalarial. The antibacterial evaluation of most compounds is underway at the moment.

CONCLUSIONS:

In conclusion, this research was successful in preparing 1-substituted benzyl models of the tetrahydroisoquinoline nucleus utilizing Grignard coupling of 3,4-dihydroisoquinoline **(3a)** with substituted benzyl chloride tails **(4a-g)** at carbon 1 of the tetrahydroisoquinoline unit. Best conditions were to stir a mixture of magnesium turnings, iodine crystals, few drops of 1,2-dibromo ethane in THF and the substituted benzyl chloride tail at –10°C, followed by adding **3a** in THF at –80°C. An alternative strategy based on lithiation of *N*-Benzoyl-1,2,3,4-tetrahydroisoquinoline **13** followed by alkylation of the selected tails produced **5e** and **5f** with satisfactory yields upon hydrolysis of **16**. All products and intermediates were isolated, purified and their structure confirmed using NMR, IR, EA and MS techniques.

The antibacterial activity against tetracycline-resistant MRSA revealed that some compounds were identified as being of potential interest. In particular, compounds **9**, **5e** and **16** showed interesting antibacterial activity with MIC ranges of 10 to 64 μg/ml.

EXPERIMENTAL

TLC was carried out using Polygram ®SilG/UV$_{254}$ plates (silica gel 0.25 mm thick). Compounds were visualised under UV light (254nm and 366nm), exposure to iodine, and spraying with vanillin/sulphuric acid reagent. Flash chromatography was carried out on silica gel 60 (230-400 mesh). Melting points were determined on Gallenkamp and Reichert (Germany) melting point apparatus and are expressed in degrees celsius (°C).

Infrared spectra (IR) were recorded on a Matson Genesis series FT-IR spectrophotometer (USA) using potassium bromide (KBr) discs for solid samples, and liquid films on sodium chloride (NaCl) discs for oily samples. The wave frequencies, ν_{max} (cm^{-1}) are expressed for each peak representing a functional group. The nature of the band has been abbreviated as follows:

(br) broad, (s) strong, (m) medium, (w) weak, (str) stretching, (def) deformation, (asym) asymmetrical, (sym) symmetrical.

Low and high resolution mass spectra (MS) were determined on a JEOL DX303 spectrometer (Japan) for electron impact (+ EI) analysis and fast atom bombardment (FAB) at Strathclyde university/ UK. Proton nuclear magnetic resonance (^{1}H and ^{13}C-NMR) spectra were determined on Bruker WM 250 (250 MHz) and Bruker AMX-400 (400MHz) spectrometers (Germany) as indicated in the text at Strathclyde University-UK. Chemical shifts are expressed in parts per million (ppm) as δ values. All solvents used were deuterated. Most samples were run using $CDCl_3$, unless indicated otherwise.

Chemicals and reagents:

Chemicals and reagents used were obtained from Aldrich Chemicals UK Ltd and Across Ltd (UK). Solvents and reagents were of general grade unless stated otherwise.

(7a) *N*-Phenethyl formamide [17]

Phenylethylamine (5.0g, 0.0413mol) was dissolved in ethanol (50ml) and placed in a 150ml round bottom flask. Ethyl formate (15ml) was then added to the reaction mixture. The mixture was heated to reflux temperature (78°C) for 48 hours with stirring. The solvent was removed *in vacuo* to give the crude product as a yellow oil (4.8g). The crude product was dissolved in chloroform and extracted using dilute HCl. The chloroform layer was collected, dried, filtered and reduced *in vacuo* to give the formamide as a yellow oil (4.60g, 75%). ^{1}H NMR: 400MHz δ ($CDCl_3$, 323K): 2.77 (2H, t, J=7.2Hz, Ar-CH_2-CH_2-N-), 3.51 (2H, t, J=6.8Hz, Ar-CH_2-CH_2-N-), 6.35 (1H broad s, NH), 7.13-7.35 (5H, m, Ar-H), 8.03 (1H, s, NH-COH); ^{1}H NMR: 400MHz δ ($CDCl_3$, R.T): 2.77 (2H, d-t, J=7.2Hz, Ar-CH_2-CH_2-N-), 3.37-3.42 (0.34H, q, J=6.8Hz, Ar-CH_2-CH_2-N-), 3.47-3.53 (1.66H, q, J=6.8Hz, Ar-CH_2-CH_2-N-), 6.05 (0.17H. broad s, NH), 6.35 (0.82H. broad s, NH), 7.12-7.33 (5H, m, Ar-H), 7.80 (0.17H, d, J=11.9Hz, N-COH), 8.03 (0.83H, d, J=1.5Hz, N-COH); HRMS: EI m/z (%): 149.08470 (M^+, 8). Calculated 149.08406, $C_9H_{11}NO$; IR: NaCl Disc υ_{max} (cm^{-1}): 3276, br-w, (N-H str), 3046, m, (Ar C-H str), 2924, 2857, m, (aliphatic C-H str), 1660, 1654, (amide C=O str, N-H def), 1591, s, (ar C=C str), 1469, s, (ar. C=C str), 755.

(3a) 3,4-Dihydroisoquinoline[16,17]

N-Phenethyl formamide (4.467g, 0.029mol) was treated with polyphosphoric acid (PPA, 50g) in a 100ml round bottom flask. The reaction mixture was heated in a sand bath to 200-220°C with stirring for 1 hour. The mixture was allowed to cool down to 50°C, then poured into iced NaOH solution (10% w/v, 1L) with vigorous stirring. The black mixture was extracted using chloroform (3x100ml). The chloroform layer was collected, dried over anhydrous magnesium sulphate, filtered and reduced *in vacuo* to give the isoquinoline as a brown oil (3.90g, 99%). MP: 49-50°C, ether. ^{1}H NMR: 400MHz δ ($CDCl_3$, R.T) : 2.71 (2H, t, J=7.8 Hz, Ar-CH_2-CH_2-N-), 3.74 (2H, t, J=7.4Hz, Ar-CH_2-CH_2-N-), 7.13-7.15 (1H, d, Ar-H), 7.22-7.36 (3H, m, Ar-H), 8.32 (1H, t, J=2.1Hz,-CH=N); ^{13}C NMR: 400MHz δ ($CDCl_3$, R.T): 31.6, 44.1 (CH_2CH_2N), 124.5, 128.2, 128.8, 130.7, 135.4, 139.7, 162.3; HRMS: EI m/z (%): 131.07480 (M^+, 96). Calculated 131.07350, C_9H_9N; IR: NaCl Disc υ_{max} (cm^{-1}): 3276, br-w, (N-H str), 3060, m, (Ar C-H str), 2937, 2842, m, (aliphatic C-H str), 1625, (imine C=N str), 1571, s, (ar C=C str), 1478, s, (ar. C=C str), 754, s, ar. def).

Upon leaving the product for a long time, or exposing to high temp. (Kügelrohr distillation), a white precipitate was formed. The unknown was unstable in solution. MP:251-254°C. ^{1}H NMR: 250MHz δ ($CDCl_3$, R.T): 1.62 (1H, broad s), 2.15-2.47 (4H, m), 2.56-2.62 (2H, d, J=15), 2.74-3.08 (4H, m), 3.80 (1H, d,d, J=3.8, 12.8Hz), 4.56 (1H, d,d, J=3.9, 12.0Hz), 5.27 (1H, s), 7.05-7.25 (8H, m, Ar-H), 7.56 (1H, m); MS: EI m/z (%), (L.R): 302, 171, 131, 103.

(3b) 6,7-Dimethoxy- 3,4-dihydroisoquinoline [18]

This compound was prepared by cyclizaton of the *N*-

[2-(3,4-Dimethoxyphenyl)ethyl) formamide (7b, 3g, 0.014 mol) using similar procedure utilized for (3a). The amide was initially prepared from 2-(3,4-dimethoxyphenylethyl amine using the same procedure for 7a.

The crude mixture of 3b was extracted using dichloromethane (3x50ml). The organic layer was collected, dried over anhydrous magnesium sulphate, filtered and reduced *in vacuo* to give 3b as a yellowish oil (1.5g, 55%).

^{1}H NMR : 400MHz δ ($CDCl_3$, R.T) : 2.54 (2H, t, J=8.0 Hz, Ar-CH_2-CH_2-N-), 3.65 (2H, t, J=8.1Hz, Ar-CH_2-CH_2-N-), 3.84(6H, s, 2 x OCH_3), 6.96 (1H, s, Ar-H), 7.12 (1H, s, Ar-H), 8.23 (1H, m, J=2.2Hz, -CH=N); ^{13}C NMR: 400MHz δ ($CDCl_3$, R.T): 32.7 48.5, 55.2, 114.4, 115.8, 130.8, 133.0, 145.5, 147.8, 165.1; HRMS: EI m/z (%): 191.09350 (M^+, 70). Calculated 191.09463, $C_{11}H_{13}NO2$; IR: NaCl Disc υ_{max} (cm^{-1}): 3320, br-w, (N-H str), 3063, m, (Ar C-H str), 2935, 2845, m, (aliphatic C-H str), 1630, (imine C=N str), 1574, , s, (ar C=C str), 1479, s, (ar. C=C str) 1240, 1124, 755, s, (ar. def).

(5a) 1-Benzyl-1,2,3,4-tetrahydroisoquinoline[17] (General method)

To magnesium turnings (0.713g, 0.029mol) in a 3-necked round bottomed flask was added dry THF (15ml), and 2-3 crystals of iodine. After 10 minutes, 1-2 drops of 1,2-dibromo ethane was added, then stirring was started and continued until the color of the iodine disappeared (30 minutes). The mixture was cooled to -10°C and benzyl chloride (1.445g, 0.0114mol, in 20ml of THF) was added dropwise over 1 hour. The reaction was cooled to -78°C and 3,4-dihydroisoquinoline (1g, 7.62x10^{-3}mol) was added in 10 ml of THF over 10 minutes. Stirring was continued for 3 hours at -78°C and then overnight at room temperature. Water was added and the product was extracted with ether, dried, filtered and reduced to give a yellow oil (1.62g). The oil was poured into ethereal HCl solution, filtered, and washed with dry ether to give the solid salt. The solid was basified to obtain the 1-benzyl-1,2,3,4-tetrahydroisoquinoline as a yellow oil (1.250g, 74%). MP (HCl salt): 187-189°C, ether, Lit = 192°C[30]. ^{1}H NMR: 250MHz δ ($CDCl_3$, R.T): 1.27 (1H, broad s, NH), 2.72-2.99 (4H, m, 2x CH_2-), 3.19-3.31 (2H, m, 1x-CH_2-), 4.23 (1H, d,d, J=3.4, 9.8Hz, NH-CH-), 7.11-7.37 (9H, m, Ar-H); ^{1}H NMR: 400MHz δ ($CDCl_3$, R.T): 2.20 (1H, broad s, NH, D_2O exch.), 2.58-2.85 (4H, m, 2x CH_2), 3.03-3.21 (2H, m, 1x-CH_2-), 4.11-4.16 (1H, d,d, J=7.4, 10.0Hz, N-CH-), 7.0-7.44 (9H, m, Ar-H); ^{13}C NMR: 400MHz δ ($CDCl_3$, R.T): 29.7, 41.5, 41.6, 42.2, 56.7, 118.4, 125.5, 125.9, 126.0, 126.8, 126.9, 128.4, 128.8, 129.1, 129.4, 129.7, 135.8, 138.7, 139.6; MS: EI m/z (%): 223 (M^+, <1), 220, 133, 132 (100), 130; IR: NaCl Disc υ_{max} (cm^{-1}): 3330, broad, (N-H str) , 3061, 3019, s, (Ar C-H str), 2919, 2842, w, (aliphatic C-H str), 1665, s, (N-H def), 1600, m, (ar. C=C str), 1486, s, (ar. C=C str), 749, 793, s, (ar. def).

Oxidation of 5a to 1-benzoyl-3,4-dihydroisoquinoline 18a

Oxidation was noticed during attempted purification of 5a. A sample (30mg) of the free base was dissolved in 10 ml of chloroform and left on the bench exposed to air for 2 weeks. An intermediate oxidation product was identified using MS the enamine intermediate (221, M^+), while the final oxidised product was separated on preparative TLC plates and identified as 1-benzoyl-3,4-dihydroisoquinoline (18a). Hexane:ethyl acetate (1:1) was used as a mobile phase. Compound 18a had an Rf value of 0.68 and was identified in the mixture (15mg) as a major final product.

^{1}H NMR: 250MHz δ ($CDCl_3$, R.T): 2.86 (2H, t, Ar-CH_2.CH_2), 3.98 (2H, t, Ar-CH_2-CH_2), 6.98-7.10 (4 peaks = (2H, d (J=8.6Hz), 1H, s, 1H, s, Ar-H), 7.26 (3H, m, Ar-H), 8.06 (2H, d (J=8.7Hz), Ar-H).

(5b) 1-(4-methybenzyl)-1,2,3,4-tetrahydroisoquinoline [21]

To magnesium turnings (0.80g, 0.033mol, 3M excess) in a 3-necked round bottomed flask was added dry THF (15ml), and 2-3 crystals of iodine. After 10 minutes, 1-2 drops of 1,2-dibromo ethane was added, then stirring was started and continued until the color of the iodine disappeared (30 minutes). The mixture was cooled to -10°C and p-methyl benzyl chloride (1.5g, 0.011mol, in 20ml of

THF) was added dropwise over 1 hour. The reaction was cooled to -78°C and 3,4-dihydroisoquinoline (0.72g, 5.5x10^{-3}mol) was added in 10 ml of THF over 10 minutes. Stirring was continued for 3 hours at -78°C and then overnight at room temperature. Water was added and the product was extracted with ether, dried, filtered and reduced to give a yellow oil (1.41g). The oil was poured into ethereal HCl solution, filtered, and washed with dry ether to give the solid salt. The solid was basified to obtain the 1-(4-methylbenzyl)-1,2,3,4-tetrahydroisoquinoline as a paint oil (1.12g, 86%). MP (HCl salt): 204-206°C.

^{1}H NMR: 400MHz δ ($CDCl_3$, R.T): 2.10 (1H, broad s, NH, D_2O exch.), 2.29(3H, s, CH_3), 2.80-3.18 (4H, m, 2x CH_2-), 3.41-3.50 (2H, m, 1x-CH_2-), 4.40-4.45 (1H, d,d, J=8.1, 10.0Hz, NH-C*H*-), 7.36-7.64 (8H, m, Ar-H); ^{13}C NMR: 400MHz δ ($CDCl_3$, R.T): 28.6, 29.4, 39.2, 40.6, 42.64, 55.3, 126.1, 126.6, 126.7, 127.9, 128.2, 128.8, 130.1, 133.8, 137.4, 138.3; MS: EI m/z (%): 237.4 (M^+), 277, 220, 132 (100), 83, 57; IR: NaCl Disc υ_{max} (cm^{-1}): 3332, broad, (N-H str), 3061, 3020, s, (Ar C-H str), 2919, 2840, , w, (aliphatic C-H str), 1665, , s, (N-H def), 1600, , m, (ar. C=C str), 1486, , s, (ar. C=C str), 744, 798, s, (ar. def).

(5c)1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline [31]

To magnesium turnings (1.120g, 0.045mol, 3M excess) in a 3-necked round bottomed flask was added dry THF (15ml), and 2-3 crystals of iodine. After 10 minutes, 1-2 drops of 1,2-dibromo ethane was added, then stirring was started and continued until the color of the iodine disappeared (30 minutes). The mixture was cooled to -10°C and 4-methoxy benzyl chloride (2.38g, 0.0153mol, in 20ml of THF) was added dropwise over 1 hour. The reaction was cooled to -78°C and 3,4-dihydroisoquinoline (1.0 g, 7.62x10^{-3}mol) was added in 10 ml of THF over 10 minutes. Stirring was continued for 3 hours at -78°C and then overnight at room temperature. Water was added and the product was extracted with ether, dried, filtered and reduced to give a yellow oil (1.52g). The oil was poured into ethereal HCl solution, filtered, and washed with dry ether to give the solid salt. The solid was basified to obtain the 1-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline as a paint yellow oil (1.21g, 63%).

^{1}H NMR: 400MHz δ ($CDCl_3$, R.T) : 1.92 (1H, broad s, NH), 2.70-2.94(4H, m, 2x CH_2-), 3.14-3.23 (2H, m, 1x-CH_2-), 3.86-(3H, s, OCH_3), 4.18-2.21 (1H, d,d, J=5.4, 10.1Hz, NH-C*H*-), 6.56-6.85 (8H, m, Ar-H); IR: NaCl Disc υ_{max} (cm^{-1}): 3331, broad, (N-H str), 3065, 3019, s, (Ar C-H str), 2925, 2845, w, (aliphatic C-H str), 1666, s, (N-H def), 1605, 1488, m, (ar. C=C str), 1230, 1123, , s, (C-O-C str) 748, 790, s, (ar. def).

(5d) 1- (3,4-Dimethoxybenzyl)- 1,2,3,4-tetrahydroisoquinoline[29, 32]

To magnesium turnings (1.120g, 0.046mol, 3M excess) in a 3-necked round bottomed flask was added dry THF (15ml), and 2-3 crystals of iodine. After 10 minutes, 1-2 drops of 1,2-dibromo ethane was added, then stirring was started and continued until the color of the iodine disappeared (30 minutes). The mixture was cooled to -10°C and 3,4-dimethoxy benzyl chloride (2.86g, 0.0153mol, in 20ml of THF) was added dropwise over 1 hour. The reaction was cooled to -78°C and 3,4-dihydroisoquinoline (1.0 g, 7.62x10^{-3}mol) was added in 10 ml of THF over 10 minutes. Stirring was continued for 3 hours at -78°C and then overnight at room temperature. Water was added and the product was extracted with ether, dried, filtered and reduced to give a yellow oil (2.43g). The oil was poured into ethereal HCl solution, filtered, and washed with dry ether to give the solid salt. The solid was basified to obtain the 1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline as a paint yellow oil (1.33g, 62%). MP (HCl salt): 227-228°C, EtOH.

^{1}H NMR: 400MHz δ ($CDCl_3$, R.T): 2.51 (1H, broad s, NH), 2.65-3.01(4H, m, 2x CH_2-), 3.14-3.30 (2H, m, 1x-CH_2-), 3.86(3H, s, OCH_3), 3.88(3H, s, OCH_3), 4.12-4.19 (1H, d,d, J=4.5, 8.7Hz, NH-C*H*-), 6.55-6.92 (7H, m, Ar-H); IR: NaCl Disc υ_{max} (cm^{-1}): 3335, br m, (N-H str), 3065, 3018, 2s, (Ar C-H str), 2919, 2846, w, (aliphatic C-H str), 1668, s, (N-H def), 1610, 1487, m, (ar. C=C str), 1245, 1130, s, (C-O-C str), 745, 795, s, (ar. def).

(5g)1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[18,29]

To magnesium turnings (0.79g, 0.033mol, 3M excess) in a 3-necked round bottomed flask was added dry THF (15ml), and 2-3 crystals of iodine. After 10 minutes, 1-2 drops of 1,2-dibromo ethane was added, then stirring was started and continued until the color of the iodine disappeared (30 minutes). The mixture was cooled to -10°C and 3,4-dimethoxy benzyl chloride (1.96g, 0.011mol, in 20ml of THF) was added dropwise over 1 hour. The reaction was cooled to -78°C and 6,7-dimethoxy-3,4-dihydroisoquinoline (1.0 g, $5.23x10^{-3}$mol) was added in 10 ml of THF over 10 minutes. Stirring was continued for 3 hours at -78°C and then overnight at room temperature. Water was added and the product was extracted with ether, dried, filtered and reduced to give a yellow oil . The oil was poured into ethereal HCl solution, filtered, and washed with dry ether to give the solid salt. The solid was basified to obtain the 1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline as a paint yellow oil (1.21g, 68%). MP (HCl salt): 217-218°C, Ether.

^{1}H NMR: 400MHz δ ($CDCl_3$, R.T) : 1.80 (1H, broad s, NH), 2.68-2.48 and 2.86-2.93(4H, m, 2x CH_2-), 3.14-3.21 (2H, m, 1x-CH_2-), 3.83(3H, s, OCH_3), 3.85(3H, s, OCH_3), 3.88(3H, s, OCH_3), 3.90(3H, s, OCH_3), 4.10-4.15 (1H, d,d, J=4.5, 9.2Hz, NH-C*H*-), 6.59(1H, s, Ar-H), 6.67(1H, s, Ar-H), 6.75 (1H, s, Ar-H), 6.81 (1H, d, J= 8Hz, Ar-H), 6.85 (1H, d,d, J= 2.2, 8.1 Hz, Ar-H); ^{13}C NMR: 400MHz δ ($CDCl_3$, R.T): 29.8, 41.5, 42.4, 56.1, 57.2, 109.7, 111.5, 111.7, 112.1, 112.6, 121.2, 127.6, 131.1, 132.0, 146.6, 147.1, 148.8; IR: NaCl Disc υ_{max} (cm^{-1}): 3344, broad, (N-H str), 3055, 3019, s, (Ar C-H str), 2920, 2850, , w, (aliphatic C-H str),1665, s, (N-H def), 1615, 1488, m, (ar. C=C str), 1254, 1229, s, (CO-C str), 747, 795, 647 s, (ar. def).

(5e) 1-(4-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline[17]

A 3-necked flask with a stirring unit, separatory funnel, and a condenser was fit with a calcium chloride guard tube on top of the condenser. Magnesium turnings (0.56g, 0.023mol), 1- 2 drops of 1,2-DBE and a crystal of iodine were placed in the flask containing 15 ml of THF. In a separate flask, 4-hydroxy benzyl chloride (1.10g, $7.71x10^{-3}$mol) was dissolved in dried THF (50 ml). 25 ml of this solution was introduced to the mixture and then heated (40-45 ^oC) so that the solvent refluxed gently until the reaction commenced, followed by adding the rest portion wise . The water bath was removed and an ice bath was introduced to control the reaction. Next, the stirrer was set in motion and the whole amount of the alkyl halide was added dropwise over 30 minutes with vigorous stirring until the color of the iodine disappeared. The reaction was then cooled to –90, to –95^{o}C, then 3,4-Dihydroisoquinoline (0.50g, $3.81x10^{-3}$mol, in 10ml of dry THF) was added under nitrogen. The stirring was continued at -95^{o}C for three hours then at room temperature for 24 hours. Water (10ml) was added dropwise over 10 minutes and the mixture was extracted with chloroform (2x 50ml) upon drying the THF. The organic layers were collected, dried, filtered and reduced *in vacuo* to give a yellow brown oil (0.41g, 30%). Acid-base extraction gave a brown oil (0.05g, 5%). The product was further purified on silica plates for NMR with very low yield (3%). The product was prepared by a different method as explained later.

^{1}H NMR: 400MHz δ ($CDCl_3$, R.T): 2.12 (1H, broad, N*H*, D_2O exch.), 2.81-2.98 (4H, m, Ph-CH_2 and C*H*$_2$NH), 3.25-3.28 (2H, m, NH-CH_2C*H*$_2$), 4.15(1H, d,d, J=4.2, 9.8Hz, -C*H*-N), 5.95 (1H, br-s, OH, D_2O exch.), 6.86 (2H, d, J=8.4Hz, Ar-H), 6.96 (1H, d, J=7.5Hz, Ar-H), 7.05 (2H, d, J=8.4Hz, Ar-H), 7.11-7.21 (3H, m, Ar-H); IR: NaCl Disc υ_{max} (cm^{-1}): 3345-3295, broad, (N-H str), 3058, 3015, s, (Ar C-H str), 2930, 2845, w, (aliphatic C-H str), 1610, s, (N-H def), 1500, 1322, m, (ar. C=C str), 1250, 1020, m, (C-O-C str), 875, 815, 745, 695, s, (ar. def).

(5f) 1-(4-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline[17]

Magnesium turnings (143mg, 5.87mmol) were placed in a 3-necked flask fitted with a reflux condenser in a close system saturated with dry, deoxygenated nitrogen. THF (8ml) was added to cover the magnesium surface followed by a few crystals of iodine and the flask was kept undisturbed for 10 minutes. Stirring was started and few drops of 1,2-dibromo ethane were added at RT. Stirring was continued at R.T. until the color of the iodine disappeared. The flask was cooled to –10°C to control the vigorous reaction. After 20 minutes, benzyloxybenzyl chloride BOBC (355mg, 1.53mmol, in 20ml THF) was added dropwise over a period of 1 hour with vigorous stirring. After 30 minutes, the flask was cooled down gradually to -90 °C before adding the 3,4-dihydroisoquinoline (200mg, 1.53mmol, in 10ml of THF). The mixture was stirred for additional 2 hours at same temperature then left overnight at room temperature. (Conducting the reaction at -78°C did not give isolable product). The reaction was quenched with ammonium chloride solution (150ml), stirred for 2 hour then extracted with ether (2x 150ml). The ether layer was washed with water (60 ml), dried, filtered and reduced *in vacuo* to give a semi-solid yellow product (0.4320g). NMR of the crude oil showed starting material, the coupled product (**10**, 20% **)** and the reduced one (**11**, major 54%) in addition to small peaks indicating the formation of the product. The product was then separated on plate chromatography to give a very low yield (8%) of a brown yellow oil barely enough for NMR analysis. This product was prepared with a different method.

^{1}H NMR: 400MHz δ ($CDCl_3$, R.T): 1.92 (1H, br s, NH, D_2O exch.), 2.69-3.09 (4H, m, $-CH_2$), 3.22-3.26 (2H, d,d, J= 6, 11 Hz, $-CH_2$), 4.22 (1H, d,d, J=4.4, 10.4Hz, -CH-N), 5.06 (2H, s, $-OCH_2$), 6.96 (2H, d, J=8.0Hz, Ar-H), 7.20-7.24 and 7.31-7.5 (11H, m, Ar-H); MS: EI m/z (%): 329.17705 (M^+, 2), calculated: 329.17796, $C_{23}H_{23}NO$; 132.08164 (100). Calculated 132.08132, $C_9H_{10}N$; IR: NaCl Disc υ_{max} (cm^{-1}): 3332 m, (N-H str), 3034, 3025, s, (Ar C-H str), 2919, 2852, br, (aliphatic C-H str), 1645, s, (N-H def), 1604, 1505, m, (ar. C=C str), 1235, 1118, s, (C-O-C str), 810, 739, 694, s, (ar. def).

Oxidation of 5f to (4-benzyloxyphenyl)-(3,4-dihydroisoquinolin-1-yl)methanone 18f through enamine intermediate 17f

NMR showed mainly one compound and no starting material after acid-base extraction. However, a new spot started to appear (TLC) after a few days upon air exposure. $Rf_{product(5a)}$=0.0, $Rf_{\text{oxidized product}}$ =0.61, ethyl acetate:hexane (1:1) . The new fraction was separated on a flash silica column, using ethyl acetate:hexane, and was identified as the oxidized product (18f). The intermediate 17f was detected by MS within the first day as 1-(4-benzyloxybenzyl)-3,4-dihydroisoquinoline (EI m/z (%): 327.16096 (M^+, 21). Calculated 327.16231, $C_{23}H_{21}NO$). After 5 days of acid base extraction, the oxidized product (4-benzyloxyphenyl)-(3,4-dihydroisoquinolin-1-yl)methanone was separated on a flash silica column using ethyl acetate:hexane (1:1) as mobile phase.

^{1}H NMR: 400MHz δ ($CDCl_3$, R.T): 2.91 (2H, t, J=7.4Hz, Ar-CH_2-CH_2), 3.95 (2H, t, J=7.5Hz, Ar-CH_2-CH_2), 5.14 (2H, s, $-OCH_2$), 7.01 (2H, d,d, J=2.0, 8.5Hz, Ar-H), 7.20-7.45 (9H, m, Ar-H), 8.30 (2H, d,d, J=2.1, 8.8Hz, Ar-H); MS : EI m/z(%): 341.14149 (M^+, 5). Calculated 341.14158, $C_{23}H_{19}NO_2$: 341 (M^+, 5), 325, 250 (M^+-91, 44), 91(100); IR: NaCl Disc υ_{max} (cm^{-1}): 3054, 3028, w, (Ar C-H str), 2938, 2845, m, (aliphatic C-H str), 1664, sharp s, (C=O str), 1595, s, (C=N str), 1504, m, (ar. C=C str), 1252, 1164, s, (C-O-C str),737, s, (ar. C-H def); TLC :Hexane : ethyl acetate (1:1), Rf=0.61

1-Phenyl-2-(4′-benzyloxyphenyl)ethanol (9) [17]

All glassware and solid starting materials were oven-dried before use. THF was sodium-dried over night. Benzaldehyde and 1,2-dibromoethane (DBE) were distilled before use. Magnesium turnings (480mg, 19.74mmol) were placed in a 3-necked flask fitted with a reflux condenser in a closed system saturated with dry, deoxygenated nitrogen. THF (8ml) was added to cover the magnesium surface followed by a few crystals of iodine and the flask was kept undisturbed for 10 minutes. Stirring was started and a few drops of 1,2-dibromo ethane were added. Stirring was continued at room temp. until the color of the iodine disappeared (10 min). The flask was heated to 50°C to initiate the reaction then cooled to -10°C to control the vigorous reaction. After 30 minutes, BOBC (1200mg, 5.146mmol) dissolved in 20 ml of THF was added dropwise over a period of 1 hour with vigorous stirring at a temperature ranging from -10 to -15°C. The flask was kept stirring for a further 30 minutes at -10°C then cooled down to -80°C before adding the benzaldehyde (544mg, 5.126 mmol, in 10 ml of THF). The mixture was stirred for an additional 4 hours at -78°C then left overnight at room temperature.

The reaction was quenched with ammonium chloride solution, stirred for 3 hour then extracted with ether. The ether layer was washed with water (60 ml), dried, filtered and reduced *in vacuo* to give a semi-solid yellow product (2.540g). The crude product was triturated with hexane:chloroform (3:1, 2x 20ml) to remove all benzaldehyde. Re crystallisation from chloroform/ether gave the product as white crystals (0.560g, 36%). The yield figures were improved in another attempt where the product was recollected from the filtrated and recollected to give 42%. MP: 136-140°C

^{1}H NMR: 400MHz δ ($CDCl_3$, R.T) : 2.47 (1H, broad s, -OH, D_2O Exch.), 2.94 (1H, d,d, J=3.2, 14Hz,-CH_2-CH-), 3.25 (1H, d,d, J=9.8, 14.3Hz,-CH_2-CH-), 4.82 (1H, d,d, J=3.4, 9.8Hz,-CH_2-CH-), 4.97 (2H, s, OCH_2), 6.91 (2H, d,d, J=2.7, 8.4Hz, O-Ar-H), 7.23 (2H, d,d, J=2.3, 8.2Hz, O-Ar-H), 7.27-7.43 (10H, m, Ar-H); MS: EI m/z (%): 304.14575 (M^+, 11.4). Calculated 304.14633, $C_{21}H_{20}O_2$; IR: KBr Disc υ_{max} (cm^{-1}): 3311, broad, (OH str) 3053, 3024, w, (Ar C-H str), 2942, 2867, w, (aliphatic C-H str), 1600,1492, m, (ar. C=C str), 1240, 1014, s, (ar. C-O-C str); TLC: Hexane: ethyl acetate (3:1), Rf=0.26

Two major side products were isolated and identified. The first was purified by crystallisation from chloroform/hexane (2x), whereas the second was left in the crude mixture and was collected from a flash silica column as a yellow oil (Rf=0.67). Using a high temperature to initiate formation of the Grignard reagent led to both side products (**10** and **11**) depending on the conditions of the experiments.

1,2-bis(4 ′-benzyloxyphenyl)ethane (10): coupled side product 1[17]

Yield from the previous experiment of (**9**) is 50%
MP 152-154°C.

^{1}H NMR: 250MHz δ ($CDCl_3$, R.T) : 2.85 (4H, s, 2x -CH_2-), 5.06 (4H, s, 2x OCH_2), 6.92 (4H, d,d, J=2.1, 8.2Hz, 2x O-Ar-H), 7.12 (4H, d,d, J=2.1, 8.3Hz, 2x O-Ar-H), 7.27-7.45 (10H, m, Ar-H); MS: EI m/z (%): 394.19571 (M^+, 2.87). Calculated 394.19328, $C_{28}H_{26}O_2$; LR: 394 (9), 198 (12), 197 (100). 107 (16), 91(66); IR: KBr Disc υ_{max} (cm^{-1}): 3029, 2932, 2873, 1604,1488, 1253, 1160, s, (ar. C-O-C str); TLC : Hexane: ethyl acetate (2:1), Rf=0.0

p-tolylbenzyl ether (11): reduced side product 2[17]

Yield from the previous experiment of (**9**) is not more than 5%

^{1}H NMR: 250MHz δ ($CDCl_3$, R.T): 2.34 (3H, s, CH_3), 5.04 (2H, s, OCH_2), 6.95 (2H, d,d, J=2.0, 8.3Hz, O-Ar-H), 7.15 (2H, d,d, J=2.1, 8.4Hz, O-Ar-H), 7.31-7.56 (5H, m, Ar-H); MS: EI m/z (%): 198.10368 (M^+, 100). Calculated 198.10447, $C_{14}H_{14}O$; IR: KBr Disc υ_{max} (cm^{-1}): 3039, 2932, 1483, 1253, s, (ar. C-O-C str); TLC: Hexane: Ethyl acetate (3:1), Rf=0.65

1,2,3,4-Tetrahydroisoquinoline (12) [17]

3,4-Dihydroisoquinoline (**3a**, 3.0g. 0.038mol) was dissolved in absolute ethanol (60ml). An equimolar amount of sodium borohydride (1.44g, 0.038mol) was added to the reaction flask. The mixture was refluxed at 90°C for 1 hour, and left overnight at room temperature. Thereafter, ethanol was evaporated under reduced pressure, and the residue was extracted with ether (2x100ml). The organic layer was washed with water, dried over magnesium sulphate, filtered and reduced *in vacuo* to give the tetrahydroisoquinoline as a brown oil (4.510g, 89%).

^{1}H NMR: 400MHz δ ($CDCl_3$, R.T): 1.87 (1H, s, NH), 2.82 (2H, t, J=6.4, Ar-CH_2-CH_2-N), 3.28 (2H, t, J=6.4, Ar-CH_2-CH_2-N-), 3.98 (2H, s, Ar-CH_2-NH), 6.99-7.02 (1H, m, Ar-H), 7.10-7.17(iH, m, Ar-H); MS: EI m/z (%): 133.08956 (M^+, 3.55). Calculated 133.08915, $C_9H_{11}N$; IR: NaCl Disc υ_{max} (cm^{-1}): 3400-3200, broad, (N-H str), 3055, m, (ar. C-H str), 2918, 2891, m, (aliphatic C-H str), 1605, w, (N-H def), 1478, s, ar. C-H str).

N-Benzoyl-1,2,3,4-tetrahydroisoquinoline (13) [17]

To a solution of tetrahydroisoquinoline (10g, 0.075mol) in 50 ml of dry pyridine at 0 °C was added 15.80g (0.115mol) of benzoyl chloride over 1 hour. After an additional 3 hours at 0°C, the mixture was filtered. The filtrate was reduced *in vacuo*, taken up with dichloromethane and shaken with water (50ml). The organic layer was then washed with sodium hydroxide solution (1M, 2x20ml), hydrochloric acid (10%, 2x10ml) and brine (40ml). The organic layer was dried, filtered, and reduced to give a brown oil (17.04g). The product was purified by flash chromatography on a flash silica column (22.3cm,Lx3.8cm,W) using hexane:ethyl acetate (1:1) as mobile phase. The product was collected as a thick yellow oil (9.63g, 54%). MP: 127-129°C, ethanol.

^{1}H NMR: 250MHz δ ($CDCl_3$) (2 conformers at R.T): 2.88 (2H, broad- t, J=6.2, Ar-CH_2-CH_2-N), 3.64 (1.32H, broad s, Ar-CH_2-CH_2-N-), 3.99 (0.67H, broad s, Ar-CH_2-CH_2-N-), 4.59 (0.66H, b-s, Ar-CH_2-NH), 4.91 (1.34H, b-s, Ar-CH_2-NH), 7.17-7.30 (4H, m, Ar-H), 7.44-7.58 (5H, m, Ar-H); ^{1}H NMR: 400MHz δ (DMSO-d_6,1 conformer, 87°C): 2.90 (2H, t, J=6.2, Ar-CH_2-CH_2-N), 3.69 (2H, t, J=5.9Hz, Ar-CH_2-CH_2-N-), 4.68 (2H, s, Ar-CH_2-NH), 7.13-7.19 (4H, m, Ar-H), 7.41-7.48 (5H, m, Ar-H); ^{13}C NMR: 400MHz δ (DMSO-d_6, 57°C): 27.6 (CH_2CH_2N), 28.7 (CH_2CH_2N), 44.6 ($ArCH_2N$), 127.0, 127.1, 127.3, 127.6, 129.3, 129..5, 130.4, 134.0, 135.3 and 137.2 (C_6H_4 and C_6H_5), 170 (C=O); MS: EI m/z (%): 237.11760 (M^+, 39). Calculated 237.11536, $C_{16}H_{15}NO$; IR:NaCl Disc υ_{max} (cm^{-1}): 3057, s, (Ar C-H str), 2925, 2842, w, (aliphatic C-H str), 1630, s, (amide C=O str), 1487, s, (ar. C=C str); TLC: Hexane: ethyl acetate (1:1), Rf=0.65; NP-HPLC (analytical, hexane:ethyl acetate (70:30), 2ml/min, Hypersil 5 silica column (250x460mm), 20µl loope). Rt=2.2 min oxidised product 1 **(14)**, 3.9 min amide **(13)**, 5.4 min oxidised product 2 **(15)**.

Three major fractions were separated using normal phase chromatography NP-HPLC: Column: Semi-prep silica Si60 column, mobile phase: Hexane:ethyl acetate (70:30), Flow Rate : 4ml/min

The first fraction was identified as 2-benzoyl-3,4-dihydro-2*H*-isoquinolin-1-one (14). This compound was crystallized after separation from hexane:ethyl acetate as white crystals. MP: 132-134 °C

^{1}H NMR: 250MHz δ ($CDCl_3$, R.T) : 3.20 (2H, t, J=6.3Hz, Ar-CH_2-CH_2-N), 4.17 (2H, t, J=6.5Hz, Ar-CH_2-CH_2-N-), 7.30-7.68 (8H, m, Ar-H), 8.12 (1H, d,d, J=1.3, 7.7Hz, Ar-H, CO-C-C_8HAr); MS: EI m/z (%): 251.09540 (M^+, 52). Calculated 251.09463, $C_{16}H_{13}NO_2$; IR: KBr Disc υ_{max} (cm^{-1}): 3058, 2948, 1659, s, (C=O str), 1593, 1457; TLC : Hexane: ethyl acetate (1:1), Rf=0.75

The second fraction was identified as the amide product (13, Rf=0.65).

The third fraction was identified as N-(2-(2-formylphenyl)ethyl)benzamide (15)

^{1}H NMR: 250MHz δ ($CDCl_3$, R.T) : 3.35 (2H, t, J=6.9Hz, Ar-CH_2-CH_2-N), 3.64 (2H, q, J=6.8Hz, Ar-CH_2-CH_2-N-), 6.23 (1H, broad s, NH), 7.10-7.52 (5H, m, Ar-H), 7.71-7.79 (4H, m, Ar-H), 10.16 (1H, s, CHO); MS: EI m/z (%): 253.11023 (M^+, 5). Calculated 253.11028, $C_{16}H_{15}NO_2$; IR: NaCl Disc υ_{max} (cm^{-1}): 3351, broad, (NH str) 3058, 2932, 2926, 2780, m, (CH str of CHO), 1728, 1690,1644, br s, (amide C=O str), 1575, 1476, 1418, 1331, 1296, 1142, 1042, 923 ald CH def and Ar CH def). TLC Hexane: ethyl acetate (1:1), Rf=0.35

1- (4-Benzyloxybenzyl)- 2- benzoyl-1, 2, 3, 4-tetrahydroisoquinoline (16) [17]

To a cooled solution of the amide N-benzoyltetrahydroisoquinoline **13** (3.48.0g, 14.7mmol, in 8 ml of THF) and tetramethylethylene diamine (TMEDA, 2.2 ml, 1.69g, 14.7mmol) in 50ml THF was added t-BuLi (8.65ml,1.05 M excess, 1.7M in pentane). The resulting blue-purple solution was stirred for 20 minutes at -78°C before adding the electrophile BOBC (4.12g, 17.7mmol) dissolved in THF. After stirring for 24 hours at-78°C , the solution was hydrolyzed with water and warmed to room temp. The solvent was evaporated and the mixture was poured into water and extracted with chloroform. The combined organic layers were washed with water, dried over MgSO4, and reduced *in vacuo* to give the crude oil of **16** (4.52g, 71%).

For identification purposes, normal phase-HPLC was used. A semi-prep Si60 column was used. The mobile phase was hexane: ethyl acetate (70:30). One major peak (Rt=7.7) was collected and identified to be the 1-benzyloxy benzyl-benzoyltetrahydroisoquinoline (**16**). The 2 oxidized products were also collected and identified as (**14**) and (**15**). One peak for starting material **13** was also detected.

^{1}H NMR: 400MHz δ ($CDCl_3$, 57°C) : 2.63 (1H, d-t, Ar-CH_2-CH_2-N), 2.91-4.12 3H together (1H, m, Ar-CH_2-CH_2-N-), (1H, m, Ar-CH_2-CH_2-N-) and 4.18 (1H, Ar-CH_2-CH_2-N-), 5.09 (2H, s, OCH_2), 6.39 (1H, t, J=6.4, CH-N), 7.0-7.51(m, 18H, Ar-H); ^{13}C NMR: 400MHz δ ($CDCl_3$, 57°C): 29.15, 39.11, 40.55, 42.68, 70.32, 114.92, 126.06, 126.62, 127.58, 127.81, 127.88, 128.0, 128.21, 128.45, 128.65, 128.77, 129.88, 130.71, 131.21, 133.81, 137.47, 157.47, 176.45; MS: EI m/z (%): 433 (M^+, 12), 356, 342, 329, 91; IR: NaCl Disc υ_{max} (cm^{-1}): 3030, 2960, s, (Ar C-H str), 2861, M, (aliphatic C-H str), 1610, s, (C=O str), 1505, 1451, m, (ar C-H str), 1240, 1105, s, (C-O-C str); NP-HPLC Si60 semi-prep, hexane:ethyl acetate (70:30), 6ml/min, 5mg/ml. Rt=6.31 min oxidized product 1 **(14)**, 7.7 min product **(16)**, 20 min amide starting material **(13)**, 30.8 min oxidized product 2 **(15)**.

1-(4-Hydroxybenzyl) -1,2,3,4-tetrahydroisoquinoline (5e)

A mixture of 1-benzyloxybenzyl-2-benzoyl-tetrahydroisoquinoline (**16**, 1.0g, 2.31 x10^{-3}mol), concentrated hydrochloric acid solution (50ml), and absolute ethanol (50 ml) was heated under reflux overnight. The mixture was kept stirring for 39 hours under a nitrogen atmosphere. Water (20ml) was added and ethanol was evaporated under reduced pressure. The mixture was dissolved in ether (100 ml), dried over sodium sulphate, filtered and reduced to give the crude oil (0.92g). The oil was poured into ethereal-HCl solution, and the salt was filtered off and washed with 50ml of ether. The salt was basified and extracted with chloroform to give 1-(4-Hydroxybenzyl) -1,2,3,4-tetrahydroisoquinoline **(5e)** (yellow oil, 0.45g, 82%) (for data see **5e**).

1-(4-benzyloxy benzyl)-1,2,3,4-tetrahydroisoquinoline (5f)

To a solution of N-benzoyl-1-(4-benzyloxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**16**, 1.0g, 0.0023mol, in 40 ml of dry THF) stirred at 0°C was added a solution of $NaAlH_4$ (262mg, 0.0048mol, 2.1M excess, in 25 ml of dry THF). The mixture was allowed to warm slowly to R.T., then it was stirred and heated (30-40 °C) for 24 hours under nitrogen atmosphere. The reaction was left for a further 2 days. Water (20ml) was added followed by ether (100ml), then the amine was first extracted into the aqueous layer with dilute hydrochloric acid (2N, 100ml), separated, and the salt was basified with potassium hydroxide solution (10%, w/v) and extracted with chloroform (3x150ml). After drying ($MgSO_4$) and evaporating, the product was collected as a pale yellow oil (450mg, 60%). For data see **5f**.

Antibacterial screening:

The assay used involved a simple protocol for measurement of Minimum Inhibitory Concentration (MIC) using 0.3 ml 96 well-microtitre plates. The procedure used is as follows:

- One litre of Mueller Hinton broth (MHB) (Oxoid) was prepared and adjusted to contain Ca^{2+} (20 mg/L) and Mg^{2+} (10 mg/L). The mixture was sterilised in an autoclave. The side of a 96 well-microtitre plate (Nunclon) (0.3 ml well volume) was labeled with 10 concentrations (512 – 1 mg/ml) with one well for sterility control and one well for growth control. This was followed by transferring 125 ml of Mueller Hinton broth (MHB) to all wells of the microtitre plate except for the sterility control well. Then, 125 ml of the stock antibiotic solution (2048 mg/ml) was added to the well-labeled 512 mg, mixed and transferred (125 ml) to the next well. The dilution was repeated to the last tube except for the growth control tube and the final volume was placed into the sterility control well.
- The inoculums was prepared by taking a slope of test organism and adding 2 ml of sterile normal saline with the use of a sterile loop to generate a turbid solution. 100 ml of this solution was taken and added to 10 ml of sterile saline. This solution was compared with the 0.5 McFarland turbidity standard*, and adjusted if necessary. This would give a suspension of 108 cfu/ml. The solution was diluted 10 fold and then 20 fold to give a solution of 5 x105 cfu (the transparent solution).
- 125 ml of test organism (approximately 5 x 105

cfu/ml) was added to each well and the plate was incubated at 36°C for 18 hrs. The MIC endpoint was read at the lowest concentration of antibiotic at which there is no visible growth.

* Tatrazolium solutions may be added to visualize end point.

* A 0.5 McFarland standard was prepared by adding 0.05 ml of barium chloride solution (1.175% (w/v) aqueous solution) to 9.95 mls of sulphuric acid solution (1%), with constant agitation. This standard will have the same turbidity as a bacterial suspension with 108 cfu/ml.

* The modulation assay is the same as above but test compounds are incorporated into the medium at 10 micrograms/ml.

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تصنيع مشتقات من مجموعة 1-بنزيل-4،3،2،1-تتراهايدرو ايسو كوينولين الجزء الأول: استخدام تفاعل جرينيارد لتصنيع مشتقات من مجموعة 1-بنزيل-4،3،2،1-تتراهايدرو ايسو كوينولين ذات فعالية محتملة ضد البكتيريا

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ملخص

تعد مجموعة القلويدات بنزيل تتراهايدروايسوكوينولين مجموعة ذات فعالية بيولوجية. يهدف هذا العمل لاستخدام تفاعل جرينيارد والتحقق في الظرف المناسب لتحضير بعض المركبات المعروفة او الجديدة او الطبيعية ومسح فعاليتها البيولوجية. تم ربط المركب 4،3-دايهايدروايسوكوينولين (الرأس **3a**) بالمركبات الذنبية بنزيل كلوريد (**4a-d**) باستخدام تفاعل جرينيارد، تبين بعد عدة محاولات أن أحسن الظروف هي خلاط مغنيسيوم صلب، حبيبات يود، ومادة 2،1-دايبروموايثين في الايثر المعروف THF كمذيب مع البنزيل كلوريد (4) على درجة حرارة -10 مئوية ثم إضافة الرأس 3a على درجة -80 مئوية. نجحت هذه الطريقة في تحضير المركبات **5a-d** وأعطت كمية قليلة جدا من المركبات **5e-f** وعلى درجة حرارة أقل. تم تحضير المركبين 5e، 4f بطريقة الليثيشن لـ ن-بنزويل-4،3،2،1-تتراهايدروايسوكوينولين 13 متبوعاً بإضافة الذنب **4e، 4f** (اللكيليشن) لإنتاج 5f و5e بكميات معقولة. أظهرت بعض المركبات فعالية ملحوظة ضد البكتيريا المقاومة للتتراسيكلين نوع MRSA وخاصة مركبات **16, 5e, 9**. لقد نجح هذا البحث في تحضير مشتقات جديدة من نوع بنزيل تتراهايدروايسوكوينولين والتي اظهرت فعالية ضد بعض انواع البكتيريا.

الكلمات الدالة: تتراهايدروايسوكوينولين، بنزيل تتراهايدروايسوكوينولين، تفاعل جرينيارد، مقاومة البكتيريا.

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