

Synthesis Of Novel 1,2,3,4-Tetrahydro-Isoquinoline Derivatives

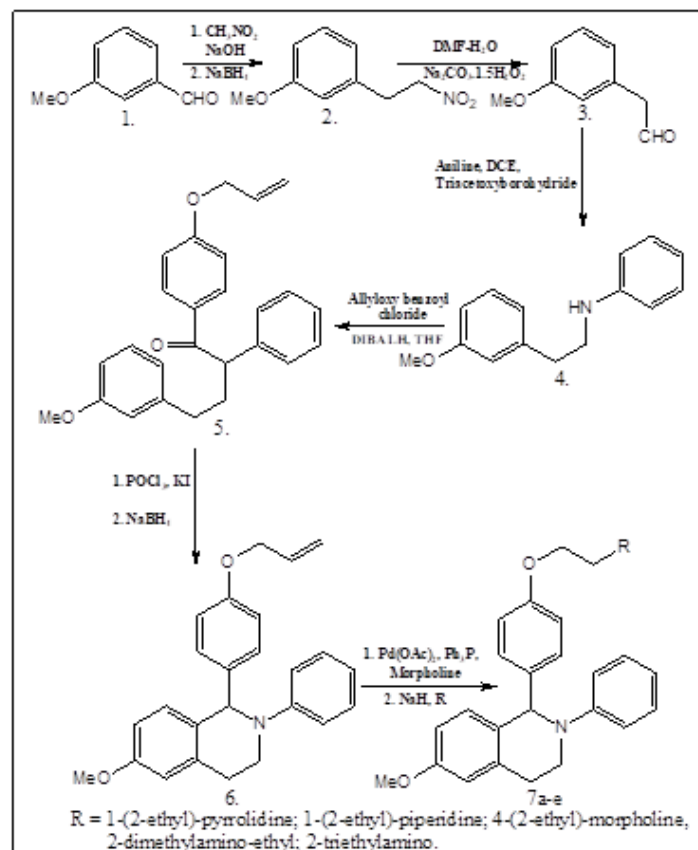
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Abstract: Novel substituted 1,2,3,4-tetrahydro-isoquinoline derivatives have been synthesized with pyrrolidine, piperidine, morpholine, dimethyl and triethyl as substituents. The synthesis follows a multistep reaction route involving Henry reaction, Nef reaction, reductive amination, amidation and N-alkylation. The synthesized compounds were designed as potent pharmacological agent. The synthetic route gives molecules in decent yields (80%-90%).

Index Terms: 1,2,3,4-tetrahydro-isoquinoline, Henry reaction, Nef reaction, pyrrolidine, piperidine, morpholine, N-alkylation.

1. INTRODUCTION

Isoquinolines are heterocyclic, aromatic, structural isomers of quinolines. It is a benzopyridine in which 'N' atom is not directly attached to the benzene ring. It is a colourless, hygroscopic liquid with penetrating, unpleasant odour [1]. Isoquinoline core finds its presence in many natural alkaloids like papaverine [2], berberine [3], curcyleatjehine [4], ecteinascidin [5], cryptaustoline [6], labrandine [7], roebramine [8], chaetoindicin A [9], neocaryachine [10]. Isoquinolines show multiple bioactivities, like dimethisoquin [11] acts as anaesthetic; quinapril [12], debrisoquine [13] acts as antihypertensive agent; 2,2'-hexadecamethylenediisoquinolinium dichloride [14] acts as antifungal and antiseptic agent; N-laurylisoquinolinium bromide [15] acts as disinfectant; papaverine acts as vasodilator. Besides this pyrrolidine cores are also pharmacologically active scaffolds. They show multifarious bioactivities and act as antidiabetic [16], anticancer [17], antimalarial [18], antiviral [19], antimicrobial [20], anti-inflammatory [21], antibacterial agents [22]. The novel molecules were designed with the idea of conjoining the pharmaceutically potent scaffolds of tetrahydroisoquinoline with pyrrolidine, in order to produce a more effective and potent drug molecule. The design and framework of the molecules was kept such that it mimicked the molecular structure that can also interact with estrogen receptors and thereby act as potent selective estrogen receptor molecules. The novel approach for tetrahydroisoquinoline synthesis involves Henry reaction followed by reduction of the intermediate yielding 1-methoxy-3-(2-nitroethyl)benzene. This was then followed by Nef reaction and reductive amination, affording [2-(3-Methoxy-phenyl)-ethyl]-phenyl-amine; superseded by amidation in presence of allyloxy benzoyl chloride yielding 4-Allyloxy-N-phenethyl-N-phenyl-benzamide. This further reacts with $\text{POCl}_3/\text{KI}/\text{NaBH}_4$ giving rise to 1-(4-Allyloxy phenyl)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline. The relay of this synthetic route is displayed through Scheme 1.



Scheme 1: Synthetic route for novel tetrahydroisoquinoline derivatives

2 EXPERIMENTAL

2.1 Material and Method:

All synthesis work was performed in clean, oven-dried Borosil glasswares. Analytical grade chemicals and reagents were purchased from Sigma Aldrich and used for this synthesis work. Reactions were tracked and observed through Thin-layer chromatography (TLC) [23] performed on TLC silica gel plates with specification 60 F₂₅₄ by Merck and visualized under UV illuminator chamber. Melting points were calculated using capillary tubes in melting point apparatus. IR spectra were recorded on Perkin Elmer IR recorder. ¹H-NMR and ¹³C-NMR

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analysis was performed at 500MHz and 125MHz respectively, on JNM-ECZ500R/S1 spectrophotometer using deuterated chloroform as solvent. High resolution mass spectra were documented using Agilent 6520 (Q-TOF).

2.2 General Procedure for Synthesis of Target Molecule:

2.2.1 General Procedure for Synthesis of 1-methoxy-3-(2-nitroethyl)benzene {2}:

0.016mole of nitromethane (0.9766gm.) was taken in a round bottom flask, connected to a reflux assembly and 0.016mole of methoxybenzaldehyde (2.1784gm.) was added to it, drop wise; in presence of 10-15ml. of 10% NaOH. A solid precipitate of 1-methoxy-3-(2-nitroethyl)benzene was isolated. 0.01mol. sodium borohydride (3.783gm.) was dissolved in 20ml. of ethanol and this slurry was stirred for 20minutes in cold (0-5°C). Thereafter, 0.1mol. of 1-methoxy-3-(2-nitroethyl)benzene in 20ml. of ethanol was added to it. The mixture was stirred in cold for 1 hour and then at room temperature for 3-4 hours, giving a pale yellowish precipitate. The precipitate was filtered and recrystallized with diethyl ether to yield 1-methoxy-3-(2-nitroethyl)benzene {2}.

2.2.2 General Procedure for Synthesis of (3-methoxyphenyl)acetaldehyde {3}:

0.03mol. 1-methoxy-3-(2-nitroethyl)benzene (4.86gm.) was dissolved in (15% V/V) DMF-H₂O solution. 19.0mmol (3.0gm.) of sodium percarbonate (Na₂CO₃·1.5H₂O₂) was also dissolved in it, with 500mg. of 100-200 mesh silica gel. The reaction mixture was capped using a reflux condenser with a guard tube filled with anhydrous calcium chloride, fixed at its top. The reaction mixture was then stirred for an hour at 40°C and the reaction progress was followed through TLC. After the completion of reaction (approx. 2.5hrs.) 10ml. water was added to the reaction mixture and the product was extracted into ether (3 X 10ml.) and finally dried over sodium sulfate. The ethereal solution was then subjected to reduction under vacuum and the obtained crude product was purified through column chromatography to afford (3-methoxyphenyl)acetaldehyde {3}.

2.2.3 General Procedure for Synthesis of [2-(3-Methoxyphenyl)-ethyl]-phenyl-amine {4}:

10mmol of (3-methoxyphenyl)acetaldehyde (1.5gm.) was taken in a R.B. flask with 20mmol of aniline (1.82ml.) in 35ml. of 1,2-dichloroethane (DCE) and then the reaction mixture was treated with 14mmol sodium triacetoxymethylborohydride (3gm.). The reaction mixture was stirred at room temperature under inert atmosphere for 6hrs. and the progress of the reaction was monitored through TLC. After reaction completion, the product was extracted through ethyl acetate, dried over sodium sulphate and evaporated under vacuum. The product [2-(3-Methoxyphenyl)-ethyl]-phenyl-amine {4} obtained, was subjected to column chromatography for purification.

2.2.4 General Procedure for Synthesis of 4-Allyloxy-N-phenethyl-N-phenyl-benzamide {5}:

12.5mmol. of [2-(3-Methoxyphenyl)-ethyl]-phenyl-amine was taken in a completely dry R.B. flask and 10ml. THF was added to it. After cooling the reaction mixture to 0°C, 1.2mmol DIBALH [1.2ml. (diisobutylaluminumhydride 1M in hexane)] was added drop wise to the reaction mixture for 3hrs. maintaining the temperature upto 0-5°C. 10mmol allyloxy

benzoyl chloride (1.63ml.) was added dropwise to this reaction mixture and stirred for 10 minutes and 10ml. of 1N HCl solution was added to it. The product was extracted with diethyl ether (2 X 10ml.) and the ethereal layer was dried over sodium sulphate, the extract was then subjected to evaporation under vacuum, to yield 4-allyloxy-N-phenethyl-N-phenyl-benzamide {5}.

2.2.5: General Procedure for Synthesis of 1-(4-Allyloxy phenyl)-6-methoxy-2-phenyl-1,2,3,4-tetrahydro-isoquinoline {6}:

3.39gm. of synthesized 4-Allyloxy-N-[2-(3-methoxyphenyl)-ethyl]-N-phenyl-benzamide was taken in R.B. flask with 0.93ml. POCl₃ and 0.16gm. KI. The entire system was refluxed for 6hrs. followed by addition of 0.037gm. of sodium borohydride for facilitating in situ reduction. The reflux was continued for 20-30 mins. and ultimately a semi-solid mass was isolated. The crude compound was subjected to chromatography (1:6::ethyl acetate:hexane) in order to obtain pure 1-(4-Allyloxy phenyl)-6-methoxy-2-phenyl-1,2,3,4-tetrahydro-isoquinoline {6}.

2.2.6 General Procedure for Synthesis of 6-Methoxy-2-phenyl-1-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1,2,3,4-tetrahydro-isoquinoline {7a-7e}:

3.71gm. of 1-(4-Allyloxy phenyl)-6-methoxy-2-phenyl-1,2,3,4-tetrahydro-isoquinoline was taken in dimethyl formamide (DMF) and subjected to reduction using palladium diacetate (4-6mol%) and potassium formate (1.68gm.) and stirred at 40-60°C for 4-6hrs. The reduced product was obtained and subjected to alkylation with 1-(2-chloroethyl)-pyrrolidine.HCl salt. 3.73gm. of reduced product was taken in a round bottom flask with 1.70gm. 1-(2-chloroethyl)-pyrrolidine and 1.38gm. potassium carbonate in 10-15ml. dry acetone. The entire mixture was refluxed for 5-6hrs. at 50-60°C. The obtained reaction mixture was extracted with water (3 x 10ml.) and treated with sodium sulphate for removal of traces of moisture. The reaction mixture was then vacuum dried in rotavapor and dried compound was isolated to yield 6-Methoxy-2-phenyl-1-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1,2,3,4-tetrahydro-isoquinoline.

Similar procedure was followed for 7b, 7c, 7d and 7e replacing 1-(2-chloroethyl)-pyrrolidine with 1-(2-chloroethyl)-piperidine, 4-(2-chloroethyl)-morpholine, 2-dimethylamino-ethylchloride and triethylamino chloride.

2.3. Spectral Analysis:

2.3.1. 6-Methoxy-2-phenyl-1-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1,2,3,4-tetrahydro-isoquinoline (7a): Dark brown amorphous solid; M.P.: 215-218°C. (IR: KBr, ν_{\max} . cm⁻¹): 1265 (C-O str.); 1175 (C-N str.); 1565-1480 (aromatic C-C str.); 1090 (C-O-C str.). (¹H-NMR in ppm: 500MHz; Solvent: CDCl₃): 6.47-6.51 (d, 2H); 6.59 (s, 1H); 6.61-6.95 (d, 4H); 6.65-7.08 (m, 5H); 5.19 (s, 1H); 3.68 (t, 2H); 2.78 (t, 2H); 4.04 (t, 2H); 2.65 (t, 2H); 3.73 (s, 3H); 2.25 (t, 4H); 1.59 (t, 4H). (¹³C-NMR in ppm: 125MHz; Solvent: CDCl₃): 159.4, 156.3, 144.5, 141.7, 134.7, 134.5, 129.3, 129.2, 129.0, 118.0, 114.7, 141.1, 114.0, 113.1, 61.3, 56.0, 53.9, 51.9, 31.4, 23.5. (MS, m/z): 428 (M⁺); 429 (M+1).

2.3.2. 6-Methoxy-2-phenyl-1-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-1,2,3,4-tetrahydro-isoquinoline (7b): Light brown amorphous solid; M.P.: 220-225°C. (IR: KBr, ν_{\max} . cm⁻¹): 3060 (C-H str.); 1275 (C-O str.); 1190 (C-N str.); 1578-1470

(aromatic C-C str.); 1095 (C-O-C str.). (¹H-NMR in ppm: 500MHz; Solvent: CDCl₃): 6.49-6.67 (d, 2H); 6.51 (s, 1H); 6.65-6.95 (d, 4H); 6.89-7.05 (m, 5H); 4.94 (s, 1H); 2.54 (t, 2H); 4.17 (t, 2H); 2.87 (t, 2H); 3.73 (s, 3H); 2.24 (t, 4H); 1.52 (m, 4H); 1.48 (m, 2H). (¹³C-NMR in ppm: 125MHz; Solvent: CDCl₃): 159.2, 156.1, 14.3, 141.0, 134.6, 129.2, 128.8, 118.0, 114.5, 113.0, 72.0, 61.3, 58.0, 55.9, 54.2, 52.6, 26.2, 25.6. (MS, m/z): 442 (M⁺); 443 (M+1).

2.3.3. 6-Methoxy-1-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-2-phenyl-1,2,3,4-tetrahydro-isoquinoline (7c): Chrome yellow amorphous solid; M.P.: 230-232°C. (IR: KBr, ν_{\max} , cm⁻¹): 3090 (C-H str.); 1295 (C-O str.); 1210 (C-N str.); 1590-1495 (aromatic C-C str.); 1100 (C-O-C str.). (¹H-NMR in ppm: 500MHz; Solvent: CDCl₃): 6.51-6.69 (d, 2H); 6.56 (s, 1H); 6.67-6.98 (d, 4H); 6.92-7.10 (m, 5H); 5.06 (s, 1H); 3.72 (t, 2H); 2.89 (t, 2H); 4.78 (t, 2H); 3.03 (t, 2H); 3.67 (t, 4H); 2.67 (t, 4H). (¹³C-NMR in ppm: 125MHz; Solvent: CDCl₃): 159.7, 156.8, 144.7, 135.1, 134.8, 129.7, 128.9, 118.7, 114.8, 114.4, 113.9, 72.8, 71.9, 61.6, 58.5, 56.9, 56.2, 31.8. (MS, m/z): 444 (M⁺); 445 (M+1).

2.3.4. {2-[4-(6-Methoxy-2-phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-phenoxy]-ethyl}-dimethyl-amine (7d): Pale yellow amorphous solid; M.P.: 200-210°C. (IR: KBr, ν_{\max} , cm⁻¹): 2950 (C-H str.); 1240 (C-O str.); 1210 (C-N str.); 1530-1450 (aromatic C-C str.); 1070 (C-O-C str.). (¹H-NMR in ppm: 500MHz; Solvent: CDCl₃): 6.42-6.50 (d, 2H); 6.52 (s, 1H); 6.57-6.91 (d, 4H); 6.78-7.02 (m, 5H); 4.98 (s, 1H); 3.52 (t, 2H); 2.56 (t, 2H); 3.67 (s, 3H); 4.01 (t, 2H); 2.89 (t, 2H); 2.37 (s, 6H). (¹³C-NMR in ppm: 125MHz; Solvent: CDCl₃): 160.2, 157.1, 145.3, 141.8, 134.7, 134.4, 129.5, 129.2, 129.0, 118.2, 114.7, 114.2, 113.2, 71.8, 58.9, 58.0, 57.1, 41.5, 31.8. (MS, m/z): 402 (M⁺), 403 (M+1).

2.3.5. Diethyl-{2-[4-(6-methoxy-2-phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-phenoxy]-ethyl}-amine (7e): Yellow coloured solid; M.P.: 210-215°C. (IR: KBr, ν_{\max} , cm⁻¹): 2920 (C-H str.); 1225 (C-O str.); 1198 (C-N str.); 1520-1440 (aromatic C-C str.); 1055 (C-O-C str.). (¹H-NMR in ppm: 500MHz; Solvent: CDCl₃): 6.45-6.54 (d, 2H); 6.56 (s, 1H); 6.59-6.89 (d, 4H); 6.80-7.06 (m, 5H); 5.01 (s, 1H); 3.48 (t, 2H); 2.87 (t, 2H); 3.66 (s, 3H); 4.01 (t, 2H); 2.79 (t, 2H); 2.40 (q, 4H); 1.01 (t, 6H). (¹³C-NMR in ppm: 125MHz; Solvent: CDCl₃): 159.8, 156.9, 145.1, 141.4, 134.4, 134.1, 129.4, 129.0, 118.1, 114.4, 114.0, 113.1, 72.0, 61.3, 58.0, 56.2, 53.9, 46.7, 13.7. (MS, m/z): 430 (M⁺), 431 (M+1).

3 RESULT AND DISCUSSION

The chemistry of the synthesized molecules integrate Henry reaction followed by Nef reaction, proceeded with reductive amination and amidation processes and ultimately ending up with N-alkylation of the synthesized molecules. The synthesis route is a multistep reaction involving six intermediates and finally yielding substituted 1,2,3,4-tetrahydroisoquinoline derivatives.

The substituents and yields of the synthesized compounds are summarized in Table 1.

Table 1: Substituents and yield % of synthesized compounds.

1.	6-Methoxy-2-phenyl-1-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1,2,3,4-tetrahydro-isoquinoline		7a	80
2.	6-Methoxy-2-phenyl-1-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-1,2,3,4-tetrahydro-isoquinoline		7b	86
3.	6-Methoxy-1-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-2-phenyl-1,2,3,4-tetrahydro-isoquinoline		7c	83
4.	{2-[4-(6-Methoxy-2-phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-phenoxy]-ethyl}-dimethyl-amine		7d	88
5.	Diethyl-{2-[4-(6-methoxy-2-phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-phenoxy]-ethyl}-amine		7e	90

The yields of the synthesized compounds are fairly well as summarized in Table 1. The substituents have also been defined in Table 1 and pyrrolidine, piperidine, morpholine, dimethyl and triethyl substituted 1,2,3,4-tetrahydro-isoquinoline molecules have been synthesized.

4 CONCLUSION

This work defines synthetic route for novel 1,2,3,4-tetrahydro-isoquinoline derivatives synthesized via a multi-step reaction route involving various intermediates and reagents. The chemistry of synthesis involves Henry reaction, Nef-carbonyl synthesis, reductive amination, amidation and N-alkylation. The synthesized molecules gave satisfactory yields (80%-90%). The synthesized molecules were characterized through their IR, ¹H NMR, ¹³C NMR and Mass spectra. The spectra conformed to the expected spectral values of synthesized molecules. Thus, the work presents synthesis of novel 1,2,3,4-tetrahydroisoquinoline derivatives in decent yields through a multistep reaction.

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S. No	SUBSTRATE	R	PROD YCT	YIELD %
1.	6-Methoxy-2-phenyl-1-(4-propoxy-phenyl)-1,2,3,4-tetrahydroisoquinoline		7a	80
2.	6-Methoxy-2-phenyl-1-(4-propoxy-phenyl)-1,2,3,4-tetrahydroisoquinoline		7b	83
3.	6-Methoxy-2-phenyl-1-(4-propoxy-phenyl)-1,2,3,4-tetrahydroisoquinoline		7c	88
4.	6-Methoxy-2-phenyl-1-(4-propoxy-phenyl)-1,2,3,4-tetrahydroisoquinoline		7d	88
5.	6-Methoxy-2-phenyl-1-(4-propoxy-phenyl)-1,2,3,4-tetrahydroisoquinoline		7e	90