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SYNTHESIS OF 1-BIPHENYL 1,2,3,4-TETRAHYDROISOQUINOLINE

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Abstract

The biological activity of isoquinoline derivatives, as analogues of various drugs, has provided great deal of interest for the synthesis of new compounds. An application of Bischler-Napieralski reaction for the synthesis of new 1,2,3,4-tetrahydroisoquinolines with biphenyl substitutent on the 1st position, is described. The required for this purpose amides would arise from reaction of aminoacetaldehyd-dimethylacetal with veratrole (1,2-dimetoxybenzene) in polyphosphoric acid, followed by acylation of obtained amines with different acid chlorides or sulfochlorides. Variety of reaction conditions – acidity of milieu, temperature and reaction time, were used for optimization the conditions for the final cyclization stage.

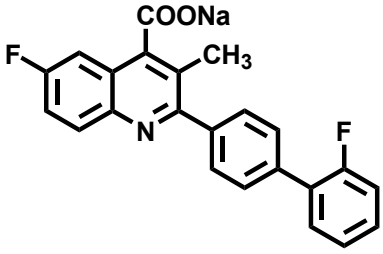
Along with the synthetic studies, structure-activity relationships will be sought (SAR and QSAR study of the compounds). Discovery of bioactivity can eventually lead to development of new therapeutic compounds. There is a possibility for application of the results in the pharmaceutical sector, should the biological properties of the obtained compounds be satisfactory for development of new drugs. The synthetic methodology which is expected to be developed will positively find future applications in the academic/research/ pharmaceutical sector.

Key words: *dihydroorotat dehydrogenase inhibitors, biphenyl substituent, tetrahydroisoquinolines*

1. INTRODUCTION

Dihydroorotate dehydrogenase (DHODH) is enzyme, identified in the Plasmodium falciparum. He is located in the mitochondrial membrane where it catalyses the oxidation of dihydroorotate to orotate, which is the rate-limiting step in pyrimidine biosynthesis[1]. Concomitant with dihydroorotate oxidation is electron transfer to ubiquinone (cofactor Q). Genes encoding all enzymes in the conserved pyrimidine pathway have been identified in the Plasmodium falciparum genome but genes encoding enzymes in pyrimidine salvage do not appear to be present. Human cells, in contrast to Plasmodium, synthesise and salvage pyrimidines.

Inhibitors of DHODH show immunosuppressant and antiproliferative activities.[2,3] Two well-described inhibitors of human dihydroorotate dehydrogenase (hDHODH) are Leflunomide and Brequinar, which are currently used to treat Malaria, rheumatoid arthritis, and analogs are in clinic to treat graft versus host disease and multiple sclerosis.



Brequinar

Inhibitors have been identified that inhibit growth of the microorganisms Helicobacter pylori and Enterococcus faecalis. They also have been investigated for anticancer activity.

In view of varied biological activities, there is a strong interest in the development of synthetic methodologies giving access to novel isoquinoline alkaloids, as potential DHODH inhibitors. In continuous need to develop new drugs we have to synthesize some nitrogen containing heterocyclic derivatives as inhibitors of DHODH, as antineoplastic agents.

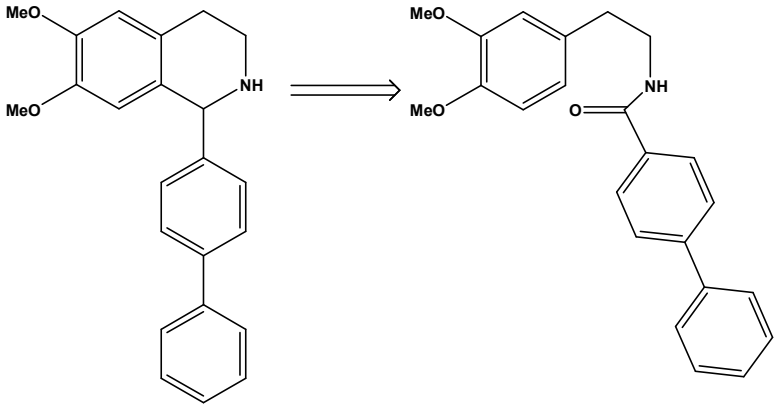
2. RESULTS AND DISCUSSION

In continuous need to develop new drugs we have to synthesize some nitrogen containing heterocyclic derivatives as inhibitors of DHODH, as anti neoplastic agents. Some of the well-known inhibitors of DHODH are quinoline and isoquinoline derivatives.

There are some new extensions for the synthesis of isoquinoline derivatives, which expand the classical methods for their synthesis - *Bischler-Napieralski*, *Pictet-Spengler* и *Pomeranz-Fritsch*. The diverse biological activities associated with the isoquinoline nuclei continue to attract a great deal of interest in their synthesis as potential new drugs. Some 1,2,3,4-tetrahydroisoquinolines may used for the synthesis of benzodiazepines, also.[4,5] A lot of other isoquinoline derivatives are important bioactive compounds.[6] They posses antimalarial,[7] neurotoxic,[8] antimicrobial, cytotoxic,[9] nematocidic,[10] limphocytic,[11] anticonvulsant[12] and anticancer[13] properties. Some isoquinoline derivatives are intermediates in the synthesis of benzodiazepines and possess antiepileptic properties.[14]

The biological activity of isoquinoline derivatives, as analogues of various drugs, has provided great deal of interest for the synthesis of new compounds. In view of the ever increasing demand for novel therapeutic agents, the proposed research is expected to be of importance mainly for the pharmaceutical sector and for the academic bio-organic sector.

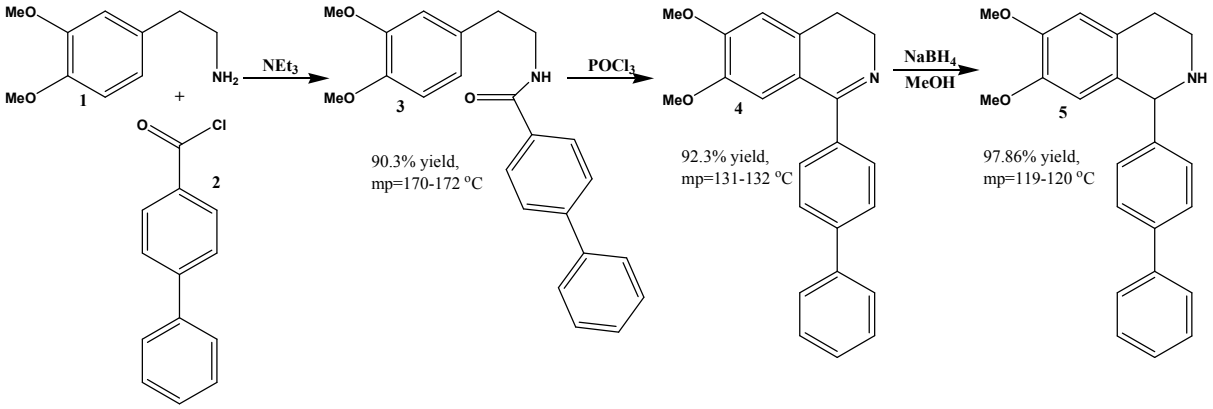
Our retrosynthetic analysis of 1,2,3,4-tetrahydroisoquinolines with biphenyl substituent on the 1st position is depicted in scheme 1. We anticipated that 1-biphenyl-1,2,3,4-tetrahydroisoquinoline **5** could be constructed from starting amides of 3,4-dimetoxy-2-phenylethylamine (homoveratrylamine) with biphenyl-4-carboxylic acid **3** via Bischler-Napieralski reaction.



Scheme 1

The required amides **3** would arise from starting homoveratrylamine **1** and biphenyl-4-carbonyl chloride **2**. Next step is cylcisation to corresponding 1-biphenyl-3,4-dihydroisoquinolines **4**. For this reaction we applied the classical Bischler-Napieralski reaction with phosphorus oxychloride as

cyclisation agent. We found that this reaction obtained dihydroisoquinolines with more then 90% yield.



For the last step, reduction of 3,4-dihydro- to 1,2,3,4-tetrahydroisoquinolines, we used mild reaction conditions using sodium borohydride/methanol reduction conditions.

Finally, we succeeded to prepare newly synthesized 1,2,3,4-tetrahydoisoquinolne derivatives with biphenyl substituent on the 1st position using simple three-step protocol using classical Bischler-Napieralski reaction for the cyclization step.

3. EXPERIMENTAL SECTION

Reagents and chemicals were purchased from commercial sources [Fluka and Merck] and used as received. Melting points were determined on a Boetius hostage apparatus and are uncorrected. Spectra were recorded on a Bruker Avance DRX250 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were taken in $CDCl_3$ at 250 MHz and 62.5 MHz respectively. Chemical shifts were given in part per million (ppm) relative and were referenced to TMS (δ=0.00ppm) as an internal standard and coupling constants are indicated in Hz. All the NMR spectra were taken at rt (ac. 295 K). TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates. Merck silica gel 60 (0.063-0.2mm) was used for column chromatographic separation

Synthesis of amide of homoveratylamine with biphenyl-4-carbonyl chloride 3.

To the solution of 1 mmol of homoveratrylamine **1** in dichloromethane equal amount of biphenyl-4-carbonyl chloride was added. After 10 min a little excess of triethylamine was added. After 30 min the solution was washed with diluted hydrochloric acid, saturated solution of Na_2CO_3 and water. The organic layer was dried (Na_2SO_4), filtered on short column with neutral Al_2O_3 and after removing of the solvent, the pure product (90.3% yield) was isolated.

^{1}H-NMR: 2.93 (t, 2H, J=6.9, CH_2), 3.75 (q, 2H, J=6.7, 6.8, CH_2), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.29 (t, 1H, J=6.2, NH), 6.80-6.88 (m, 3H, Ar), 7.38-7.51 (m, 3H, Ar), 7.60-7.67 (m, 4H, Ar), 7.79-7.82 (m, 2H, Ar); ^{13}C-NMR: 167.1, 149.1, 147.8, 144.2, 139.9, 133.3, 131.4, 128.9, 128.0, 127.3, 127.2, 127.1, 120.7, 112.0, 111.5, 55.94, 55.85, 41.3, 35.3.

Cyclisation of amide 3 to 1-biphenyl-3,4,-dihydroisoquinoline, typical procedure:

To solution of 1 mmol of amide in 1,2-dichloroethane and 1 ml posphorus oxychloride was added. The reaction mixture was refluxed for 1 h. The cool reaction mixture was washed with saturated solution of Na_2CO_3 and water. The organic layer was dried (Na_2SO_4), filtered on short column with basic Al_2O_3 and after removing of the solvent, the pure product (92.3% yield) was isolated.

^{1}H-NMR: 2.75-2.81 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.84-3.90 (m, 2H, CH_2), 3.99 (s, 3H, OCH_3), 6.83 (s, 1H, Ar), 6.91 (s, 1H, Ar), 7.36-7.52 (m, 3H, Ar), 7.68-7.76 (m, 6H, Ar); ^{13}C-NMR: 171.7, 166.3, 151.0, 147.2, 142.0, 140.6, 138.1, 132.7, 129.24, 129.22, 128.8, 127.5, 127.1, 126.8, 121.6, 111.6, 110.3, 106.0, 56.6, 56.0, 47.7, 26.1.

General procedure for reduction of dihydroisoquinoline 4. Synthesis of 6,7-dimethoxy-1-biphenyl-3,4-dihydroisoquinoline 5

To solution of 1 mmol of the 3,4-dihydroisoquinoline **4** in 15 mL methanol, $NaBH_4$ (2 mmol, 0,1 g) was added portionwise. The solution was stirred 30 min at room temperature, then the solvent was removed under vacuum. Water (30 mL) was added to the residue and the solution was extracted with CH_2Cl_2 (3x20 mL), then the combined extracts were dried (Na_2SO_4). The products, after evaporation of the solvent, were obtained with more than 95 % yields.

^{1}H-NMR: 2.23 (s, 1H, CH), 2.77 (td, 1H, J=4.9, 16.0, CH_2), 2.86-3.11 (m, 2H, CH_2), 3.23 (td, 1H, J=5.2, 11.4, CH_2), 3.65 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.10 (s, 1H, NH), 6.30 (s, 1H, Ar), 6.65 (s, 1H, Ar), 7.30-7.36 (m, 3H, Ar), 7.40-7.46 (m, 2H, Ar), 7.53-7.61 (m, 4H, Ar); ^{13}C-NMR: 147.8, 147.2, 143.7, 140.8, 140.2, 129.5, 129.3, 128.7, 127.6, 127.2, 127.1, 127.0, 111.5, 111.1, 61.0, 55.9, 55.85, 41.7, 29.2.

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