SYNTHESIS OF NEW 1, 2, 3, 4-TETRAHYDROISOQUINOLIN-1-ONE-4-CARBOXAMIDES AS CONFORMATIONALLY RESTRICTED GABA ANALOGS

MILEN G. BOGDANOV

Faculty of Chemistry, Sofia University, 1, J. Bourchier Blvd., 1164 Sofia, Bulgaria
E-mail: mbogdanov@chem.uni-sofia.bg

Abstract. A reaction between homophthalic anhydride and 2-phenyl-N-(thiophen-2-y1-methyldene)ethanamine is described. The expected 1, 2, 3, 4-tetrahydroisoquinoline-4-carboxylic acid trans-3 and Perkin by-product 4 were obtained. The carboxylic group of trans-3 was transformed in two steps into cyclic aminocarbonyl groups which yielded various new tetrahydroisoquinoliones trans-5a-i, incorporating a known fragment of pharmacological interest and various pharmacophoric substituents.

Keywords: Homophthalic anhydride, Imine, Isoquinoline, β-Amino acid, GABA.

INTRODUCTION

The transport proteins that mediate gamma-aminobutyric acid (GABA) re-uptake have been major targets for the development of agents to treat neurological diseases such as epilepsy, where augmentation of GABAergic function is indicated. β-Alanine is a relatively potent inhibitor of GAT-3 GABA transport and also serves as a substrate for the carrier and appears to interact with the transporter at the same or a similar site as GABA. It is noteworthy that the linear β-amino acid fragments are flexible and exhibit numerous conformations in solution and
even in solid state. Thus, if one can restrict the conformational freedom of these linear fragments by introducing some constraints in the structure, it may render a biologically active compound more specific and this may give rise to species, which are therapeutically useful [1]. In this direction, a number of cyclic amino acids (considered as conformationally restricted GABA analogs, see Ref.2) such as β-proline, guvacine and nipecotic acid were developed and shown to display in vitro activity as inhibitors of [3H]-GABA uptake [3]. Such a conformationally restricted β-amino acid fragment is also presented in the structure of tetrahydroisoquinolinone-4-carboxylic acids (Fig. 1). Moreover, some of these acids have shown different activities such as antiinflammatory, antiallergic, psychotropic, anti-tumor and estrogenic activity [4].

Tetrahydroisoquinolinone-4-carboxylic acids can be synthesized simply by the reaction between homophthalic anhydride (1) and an imine – a reaction proposed almost simultaneously by Haimova et al. [5a] and Cushman et al. [5b]. Continuing our attempts to further specify the scope and limitations of the reactions between cyclic anhydrides and compounds containing activated double bonds [6a-n], in this paper we present for the first time a reaction between 1 and 2-phenyl-N-(thiophen-2-yl-methylidene)ethanamine. Furthermore, we report the subsequent transformation of the carboxylic group of the obtained acid trans-3 leading to the target compounds 5a-i, incorporating both a known fragment of pharmacological interest and various pharmacophoric substituents.

RESULTS AND DISCUSSION

Several approaches are used for the synthesis of compounds containing tetrahydroisoquinoline core, but the reaction between homophthalic anhydride and imines gains advantage because of the fact that the isoquinoline core is formed in one step. The main products of the reaction – tetrahydroisoquinolonic acids possess two asymmetric centres (C3 and C4) and therefore could exist as racemic mixture of cis- or trans- diastereoisomers. The stereochemical outcome of the
reaction depends on the electronic and steric effects, the reaction conditions – solvent polarity and temperature, the presence of catalyst, and thus, the exact mechanism of the cyclocondensation process is still not clearly established. The trans-diastereomeric acids, however, can be considered as thermodynamically controlled products if the reaction is carried out under more strong conditions. Favoring the thermodynamically control of the reaction, in our case, we first carried out the reaction between 1 and 2-phenyl-N-(thiophen-2-yl-methylidene)ethanamine (2) in boiling benzene (Scheme 1). The imine 2 was synthesized simply [7a-d] by a direct condensation of thiophene-2-carbaldehyde and phenethylamine by heating at 100 °C for 15 min.

![Scheme 1](image)

In contrast to the reaction of 1 with benzalimines, the reaction of 1 and imines derived from heteroaromatic aldehydes proceeds with the formation of by-products of type 4 along with the expected cyclic acids of type 3 [6a,b]. Thus, after working up of the reaction mixture we isolated expected acid trans-3 in moderate yield (55 %) along with Perkin-type by-product 4 (yield 17 %). The formation of 4 can be attributed to decomposition of 2 to the corresponding parent aldehyde and amine in the course of the reaction. Compound 4 is known, but was previously prepared in a different manner [6c, 8]. Trying to eliminate the formation of by-product 4 the reaction was performed further in benzene and dichloromethane at room temperature, but the same ratios among the products 3 and 4 were observed. Applying ultrasonic treatment leaded to low-key the side-chain reaction and product 4 was isolated in 12 % yield. Thus, varying the reaction conditions affects slightly the course of the reaction in the case studied.

The relative configurations of the substituents at C3 and C4 in tetrahydroisoquinolonic acids could be established on the basis of coupling constants observed in proton NMR spectrum for the two protons at C3 and C4 [4–6]. In particular, compounds with cis relative configuration show two doublets with a coupling constant of ~ 6 Hz observed close to 4.0 ppm and 5.5 ppm, while in the corresponding trans-diastereoisomers the signals for H3 and H4 protons appear as
two, usually broad singlets in the same range. The $^1$H NMR spectrum of the acid 3 showed two singlets at 4.03 and 5.58 ppm for H4 and H3 respectively. On this basis we attributed trans-configuration of the acid 3.

Scheme 2

Scheme 2 gives the route of acid trans-3 to the target compounds 5a-i containing both locked β-amino acid fragment (given in bold in Fig. 1) and various pharmacophoric groups at position 4 (Table 1) of the isoquinolinone moiety that is an additional point that can modify the expected biological activity. Amides of type 5 are prepared through different synthetic strategies [9a-e]. For example, 2-(1H-7-Azabenzotriazol-1-yl)-1, 1, 3, 3-tetramethyl uronium hexafluorophosphate Methanaminium (HATU) has been used as an activation agent for the conversion of 1, 2, 3, 4-tetrahydroisoquinoline-4-carboxylic acids into amides by Ng et al. [9d]. Alternatively, compounds of type 5 have been obtained by reaction of 3-N-substituted 1H-benzo[c]pyran-1-ones and corresponding imines in acetonitrile [9a,b]. In our case, the transformation of 3 to the target compounds 5a-i was performed similarly to the protocol of Haimova et al. [10] applied to another tetrahydroisoquinoline series. Thus, the acid trans-3 was converted into acylchloride in boiling benzene in the presence of thionyl chloride. Treatment of the later with cyclic secondary amines (NuH) gave the target products. The structures of the nucleophilic groups (Nu) and the yields of the target compounds 5a-i are presented in Table 1. All synthesized compounds were isolated in solid state after recrystallization and were characterized by spectral methods (‘H-NMR- and IR-spectra) and elemental analysis.
Table 1. Structures of the nucleophytic groups Nu and the yields* of compounds 5a-i.

<table>
<thead>
<tr>
<th>Nu</th>
<th>Compd. Yield, %</th>
<th>Nu</th>
<th>Compd. Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>5a, 72</td>
<td><img src="image2" alt="Structure" /></td>
<td>5f, 75</td>
</tr>
<tr>
<td><img src="image3" alt="Structure" /></td>
<td>5b, 83</td>
<td><img src="image4" alt="Structure" /></td>
<td>5g, 72</td>
</tr>
<tr>
<td><img src="image5" alt="Structure" /></td>
<td>5c, 70</td>
<td><img src="image6" alt="Structure" /></td>
<td>5h, 63</td>
</tr>
<tr>
<td><img src="image7" alt="Structure" /></td>
<td>5e, 75</td>
<td><img src="image8" alt="Structure" /></td>
<td>5i, 80</td>
</tr>
</tbody>
</table>

* Yields after recrystallization

The description of ¹H-NMR spectra uses the arbitrary numbering given in formula 5c. The interpretation of the ¹H-NMR spectra is in agreement with the literature data for compounds of this class [9a-e] and showed the following characteristic signals: the signals for H4 and H3 protons appear as doublets within 4.18–4.92 and 4.85–5.83 ppm respectively; the two protons H12 are unequal (mentioned as 12a and 12b in the experimental section) and thus two independent signals in the region 1.10–2.00 ppm are observed for each of them; such an effect is observed for unequal protons H14 and H15; the signals for proton H8 appear at lower field (7.90–8.04) compared to the other aromatic protons. This phenomenon is an indication for proximity of H8 to the lactam carbonyl group.

The relative configuration of 5 can be attributed on the basis of the vicinal coupling constant value (Jαα) between H3 and H4 atoms in the ¹H-NMR spectra. In general, values of Jαα = 3–6 Hz suggest synclinal (sc or gauche) conformation and did not allow a distinction between cis (eq,ax in both conformers) and trans (eq,eq) configuration of H3 and H4 atoms, but knowing that the reaction does not affect the stereogenic centers and according to the observed values of Jαα of about 5 Hz we attribute trans configuration for all compounds 5 with preferred conformation with diaxial substituents at C3 and C4 atoms.

CONCLUSION

A reaction between homophthalic anhydride and 2-phenyl-N-(thiophen-2-ylmethylidene)ethanamine is presented. The reaction is highly diastereoselective towards the trans-diastereomer of 1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid...
Moreover, the transformation of the carboxylic group of trans-3 into cyclic aminocarbonyl groups is described. The later yielded various new tetrahydroisoquinolinones trans-5a-i, incorporating both a known fragment of pharmacological interest and various pharmacophoric substituents.

Acknowledgements. Financial support for this work provided by the National Science Fund, Ministry of Education and Science, Bulgaria, project TK-X-1706/07 is gratefully acknowledged.

EXPERIMENTAL

Melting points were determined on a Kofler microscope Boetius PHMK 0.5 and are uncorrected. The IR spectra were acquired in chloroform, if not stated otherwise, on a Specord 75 and are reported in reciprocal centimeters. The $^1$H-NMR spectra were obtained on a DRX Bruker Avance NMR spectrometer at 250 MHz in corresponding solvent given in parentheses. The chemical shift is given in ppm ($\delta$) relative to tetramethylsilane as internal standard. Elemental analyses were obtained in the relevant laboratories at the Faculty of Chemistry, University of Sofia. The TLC was done on precoated 0.2 mm Merck silica gel 60F$_{254}$ plates.

2-Phenyl-N-(thiophen-2-yl-methylidene)ethanamine (2).

A mixture of 12.1 g (0.1 mol, 12.6 ml) 2-phenylethylamine and 11.2 g (0.1 mol, 9.2 ml) thiophene-2-carbaldehyde was heated with steam bath at 100 °C for 15 min. The absence of the thiophene-2-carbaldehyde was detected by $^1$H-NMR. After cooling, the reaction mixture was diluted with 50 ml dichloromethane and was dried with powdered magnesium sulfate. The solvent was filtered and then evaporated under reduced pressure giving brown oil (yield 21.5 g, 100%).

$^1$H-NMR (CDCl$_3$): $\delta$ = 2.68–2.98 (2H, m, $-H,C\equiv N$), 3.42–3.78 (2H, m, $-H,C\equiv N$), 6.55–7.12 (8H, m, $H$-arom), 7.85 (1H, s, $=CH$-Th).

(±)-trans-1-Oxo-2-(2-phenethyl)-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (3)

Homophathalic anhydride (1) (16.2 g, 0.1 mol) was dissolved by heating in 200 ml of dry benzene. After all the anhydride was dissolved, the heating was stopped and the solution cooled to ambient temperature. 2-Phenyl-N-(thiophen-2-yl-methylidene)ethanamine (2) (21.5 g, 0.1 mol), dissolved in 100 ml of dry benzene, was dropwise added within 15 min. The reaction mixture was refluxed for 2 h and afterwards was left overnight at room temperature. The reaction mixture was filtered to give 4.33 g (17%), orange crystals of 4 (mp 232–233 °C, Lit.mp 232–233°C) [8]. The filtrate was diluted with ethyl acetate and extracted with 10% sodium hydrogen carbonate. The hydrogen carbonate extract was washed once with ethyl acetate, acidified (pH = 3) with 10 % hydrochloric acid and extracted three times with ethyl acetate (100 ml). The organic layers were washed with water, dried (sodium sulfate) and the solvent was removed under reduced pressure.
to give 25.3 g an oil. The oil afforded white crystals of acid trans-3. Yield 20 g
(53 %), mp 183–186 °C (from ethyl acetate). IR: 1590–1620 cm⁻¹ (ArH), 1640 cm⁻¹
(C=O), 1730 cm⁻¹ (C=O), 2500–3400 cm⁻¹ (OH); ¹H-NMR (CDCl₃): δ = 2.80–3.05
(2H, m, H-13), 3.15–3.35 (1H, m, H-12a), 4.03 (1H, s, H-4), 4.15–4.30 (1H, m, H-12b), 5.58 (1H, s, H-3), 6.78–6.89 (2H, m, H-9, H-10), 7.05–7.10 (1H, m, H-arom), 7.15–7.30 (6H, m, H-arom), 7.40–7.50 (2H, m, H-arom), 8.15 (1H, dd, J = 1.5 and 7.5Hz, H-8). Anal. Calcd. for C₁₇H₁₉NO₃S (377.46): C, 69.93; H, 5.87; N, 3.71. Found: C, 70.28; H, 5.18; N, 3.97.

**General procedure for the synthesis of compounds 5a-i.** To a suspension of acid trans-3 in dry benzene, thionyl chloride (3 equiv.) was added. The reaction mixture was stirred at 70 °C for 3 h. Then, the solvents were evaporated under reduced pressure and the residue was dissolved in dichloromethane. The cooled solution (0 °C, ice bath) was treated with the corresponding amine (3 equiv.) and was stirred for an hour. At the end of the reaction (TLC), the reaction mixture was diluted with ethyl acetate and washed with water (pH = 7). The organic layer was dried (sodium sulfate), filtered and the solvent was then evaporated under reduced pressure. The products 5a-i were isolated after recrystallization.

(±)-trans-1-Oxo-2-(2-phenylethyl)-3-(thiophen-2-yl)-1, 2, 3, 4-tetrahydroisoquinoline-4-(2-hydroxypropyl)carboxamide (5a). This compound was obtained as white crystals from ethyl acetate (yield: 0.43 g, 72 %), mp 169–172 °C; NuH: 1-amino-propan-2-ol; IR: 1590–1620 cm⁻¹ (ArH), 1640 cm⁻¹ (C=O), 1650 cm⁻¹ (C=O), 3420 cm⁻¹ (NHC=O), 3610 cm⁻¹ (OH); ¹H-NMR (CDCl₃): δ = 1.07 (3H, dd, H-C, J = 2.5 and 6 Hz), 2.85–2.96 [3H, m, H-13, -HC(OH)], 2.97–3.09 (1H, m, H-14a), 3.12–3.25 (1H, m, H-12a), 3.28–3.42 (1H, m, H-14b), 3.76 (1H, m, -OH), 3.92 (1H, s, H-4), 4.20–4.45 (1H, m, H-12b), 5.61 (1H, s, NH), 5.83 (1H, s, H-3), 6.77–6.85 (2H, m, H-Th), 7.07 (1H, dd, H-Th, J = 1.5 and 5 Hz), 7.15–7.32 (6H, m, H-arom), 7.50–7.57 (2H, m, H-arom), 8.21 (1H, d, H-8, J = 8 Hz). Anal. Calcd. for C₁₇H₁₉NO₃S (434.55): C, 69.10; H, 6.03. Found: C, 69.08; H, 6.19.

(±)-trans-2-(2-Phenylethyl)-4-(pyrrolidine-1-carbonyl)-3-(thiophen-2-yl)-3,4-dihydro-2H-isoquinolin-1-one (5b). This compound was obtained as colourless prisms from hexane/ethyl acetate-1/3 (yield: 1.24 g, 83 %), mp 87–89 °C; NuH: pyrrolidine; IR: 1590–1620 cm⁻¹ (ArH), 1635 cm⁻¹ (C=O), 1650 cm⁻¹ (C=O); ¹H-NMR (CDCl₃): δ = 1.78–2.05 (4H, m, H-16, H-17), 2.85–2.96 (1H, m, H-13), 3.12–3.26 (1H, m, H-12a), 3.36–3.60 (4H, m, H-14, H-15), 4.11–4.26 (1H, m, H-12b), 4.30 (1H, d, H-4, J = 5 Hz), 5.30 (1H, d, H-3, J = 5 Hz), 6.85–6.92 (2H, m, H-Th), 7.03 (1H, d, H-arom, J = 7.5 Hz), 7.13–7.30 (6H, m, H-arom, H-Th), 7.40–7.48 (2H, m, H-arom), 8.20 (1H, dd, H-8, J = 3 and 7 Hz). Anal. Calcd. for C₁₉H₁₇N₂O₂S (430.57): C, 72.53; H, 6.09. Found: C, 72.25; H, 6.02.
(±)-trans-4-(Morpholine-4-carbonyl)-2-(2-phenylethyl)-3-(thiophen-2-yl)-3,4-dihydro-2H-isoquinolin-1-one (5e). This compound was obtained as white crystals from ethyl acetate (yield: 0.80 g, 70 %), mp 97–99 °C; NuH: morpholine; IR: 1590–1620 cm⁻¹ (ArH), 1640 cm⁻¹ (C=O), 1650 cm⁻¹ (C=O); ¹H-NMR (CDCl₃): δ = 2.85–3.00 (2H, m, H-13), 3.38–3.70 (9H, m, H-12a, H-14, H-15, H-16, H-17), 3.85–4.10 (1H, m, H-12b), 4.32 (1H, d, H-4, J = 5 Hz), 5.05 (1H, d, H-3, J = 5 Hz), 6.60–6.80 (2H, m, H-Th), 6.90–7.40 (9H, m, H-arom, H-Th), 7.85–8.04 (1H, d, H-8, J = 8 Hz). Anal. Calcd. for C₂₉H₂₆N₂O₃S (446.63): C: 69.93; H, 5.87. Found: C: 70.31; H, 5.94.

(±)-trans-2-(2-Phenylethyl)-4-(thiomorpholine-4-carbonyl)-3-(thiophen-2-yl)-3,4-dihydro-2H-isoquinolin-1-one (5d). This compound was obtained as colourless needles from ethyl acetate (yield: 0.45 g, 75 %), mp 128–130 °C; NuH: thiomorpholine; IR: 1590–1620 cm⁻¹ (ArH), 1640 cm⁻¹ (C=O), 1650 cm⁻¹ (C=O); ¹H-NMR (CDCl₃): δ = 2.20–2.50 (2H, m, H-13), 2.60–2.82 (4H, m, H-16, H-17), 3.00–3.18 (1H, m, H-12a), 3.45–3.80 (4H, m, H-14, H-15), 3.90–4.05 (1H, m, H-12b), 4.22 (1H, d, H-4, J = 5 Hz), 4.98 (1H, d, H-3, J = 5 Hz), 6.65–6.85 (2H, m, H-Th), 6.90–7.45 (9H, m, H-arom, H-Th), 7.70–7.90 (1H, m, H-8). Anal. Calcd. for C₂₉H₂₆N₂O₃S (462.63): C: 67.50; H, 5.66. Found: C: 66.90; H, 5.18.

(±)-trans-2-(2-Phenylethyl)-4-(4-phenylpiperazine-1-carbonyl)-3-(thiophen-2-yl)-3,4-dihydro-2H-isoquinolin-1-one (5e). This compound was obtained as colourless prisms from hexane/ethyl acetate-1/2 (yield: 1.26 g, 84 %), mp 89–91 °C; NuH: 4-phenyl-piperazine; IR: 1590–1620 cm⁻¹ (ArH), 1640 cm⁻¹ (C=O), 1650 cm⁻¹ (C=O); ¹H-NMR (CDCl₃): δ = 2.85–2.96 (2H, m, H-13), 3.00–3.26 (5H, m, H-12a, H-16, H-17), 3.70–3.87 (4H, m, H-14, H-15), 4.12–4.25 (1H, m, H-12b), 4.55 (1H, d, H-4, J = 5 Hz), 5.28 (1H, d, H-3, J = 5 Hz), 6.88–6.98 (2H, m, H-Th), 7.05 (1H, d, H-arom, J = 7.5 Hz), 7.12–7.35 (11H, m, H-arom) 7.42–7.50 (2H, m, H-arom), 8.22 (1H, dd, H-8, J = 2 and 7 Hz). Anal. Calcd. for C₄₃H₃₄N₄O₂S (521.69): C: 73.68; H, 5.99. Found: C: 73.66; H, 6.02.

(±)-trans-4-[4-(2-Methoxyphenyl)piperazine-1-carbonyl]-2-(2-phenylethyl)-3-(thiophen-2-yl)-3,4-dihydro-2H-isoquinolin-1-one (5f). This compound was obtained as white crystals from ethyl acetate (yield: 0.44 g, 73 %), mp 122–123 °C; NuH: 1-(2-methoxyphenyl)piperazine; IR: 1590–1620 cm⁻¹ (ArH), 1645 cm⁻¹ (C=O), 1650 cm⁻¹ (C=O); ¹H-NMR (CDCl₃): δ = 2.60–2.98 (7H, m, H-12a, H-13, H-16, H-17), 3.18–3.60 (7H, m, H-14, H-15, -OCH₃), 3.80–3.95 (1H, m, H-12b), 4.25 (1H, d, H-4, J = 5 Hz), 4.93 (1H, d, H-3, J = 5 Hz), 6.85–7.00 (2H, m, H-Th), 7.12–7.35 (11H, m, H-arom, H-Th), 7.40–7.50 (2H, m, H-arom), 8.19 (1H, d, H-8, J = 7.5 Hz). Anal. Calcd. for C₃₇H₃₅N₃O₃S(551.70): C: 71.84; H, 6.03. Found: C: 71.76; H, 6.14.
(±)-trans-4-[4-(3-Chlorophenyl)piperazine-1-carbonyl]-2-(2-phenylethyl)-3-(thiophen-2-yl)-3, 4-dihydro-2H-isquinolin-1-one (5g). This compound was obtained as white crystals from ethyl acetate (yield: 0.43 g, 72%), mp 158–160 °C; NuH: 1-(3-chlorophenyl)piperazine; IR: 1590–1620 cm⁻¹ (ArH), 1645 cm⁻¹ (C=O), 1650 cm⁻¹ (C=O); ¹H-NMR (CDCl₃): δ = 2.55–2.98 (6H, m, H-13, H-16, H-17), 3.15–3.60 (5H, m, H-12a, H-14, H-15), 3.82–3.96 (1H, m, H-12b), 4.18 (1H, d, H-4, J = 5 Hz), 4.85 (1H, d, H-3, J = 5 Hz), 6.88–6.96 (2H, m, H-Th), 7.20–7.50 (13H, m, H-arom, H-Th), 7.90 (1H, d, H-8, J = 8 Hz). Anal. Caled. for C₃₂H₂₈ClN₂O₂S (556.12): C, 69.11; H, 5.44. Found: C, 68.86; H, 5.38.

(±)-trans-2-(2-Phenylethyl)-3-(thiophen-2-yl)-4-[4-(3-trifluoromethylphenyl)piperazine-1-carbonyl]-3, 4-dihydro-2H-isquinolin-1-one (5h). This compound was obtained as white crystals from hexane/ethyl acetate-1/3, after column chromatography (yield: 0.38 g, 63%), mp 167–169 °C; NuH: 1-(3-trifluoromethylphenyl)piperazine; IR: 1590–1620 cm⁻¹ (ArH), 1645 cm⁻¹ (C=O), 1650 cm⁻¹ (C=O); ¹H-NMR (CDCl₃): δ = 2.88–2.95 (2H, m, H-13), 3.02–3.28 (5H, m, H-12a, H-16, H-17), 3.70–3.87 (4H, m, H-14, H-15), 4.10–4.25 (1H, m, H-12b), 4.54 (1H, d, H-4, J = 5 Hz), 5.28 (1H, d, H-3, J = 5 Hz), 6.88–6.95 (2H, m, H-Th), 7.00–7.30 (10H, m, H-arom, H-Th), 7.39 (1H, t, H-arom, J = 8 Hz), 7.42–7.50 (2H, m, H-arom), 8.23 (1H, dd, H-8, J = 3 and 8 Hz). Anal. Caled. for C₃₁H₂₆F₃N₂O₂S (589.67): C, 67.22; H, 5.13. Found: C, 66.94; H, 5.06.

(±)-trans-4-[4-(4-Fluorophenyl)piperazine-1-carbonyl]-2-(2-phenylethyl)-3-(thiophen-2-yl)-3, 4-dihydro-2H-isquinolin-1-one (5i). This compound was obtained as white crystals from hexane/ethyl acetate-1/3 (yield: 1.2 g, 80%), mp 147–149°C; NuH: 1-(4-fluorophenyl)piperazine; IR: 1590–1620 cm⁻¹ (ArH), 1650 cm⁻¹ (C=O), 1660 cm⁻¹ (C=O); ¹H-NMR (CDCl₃): δ = 2.70–3.15 (6H, m, H-13, H-16, H-17), 3.40–4.10 (6H, m, H-12, H-14, H-15), 4.38 (1H, d, H-4, J = 5 Hz), 5.05 (1H, d, H-3, J = 5 Hz), 6.80–7.00 (2H, m, H-Th), 7.10–7.55 (13H, m, H-arom, H-Th), 7.85–8.00 (1H, m, H-8). Anal. Caled. for C₁₂H₁₆F₁₂N₂O₂S (539.68): C, 71.22; H, 5.60. Found: C, 71.28; H, 5.55.

REFERENCES


Received on 1 December, 2008