

SYNTHESIS OF 7-ETHYL-1,2-DIHYDROQUINOLIN-2-ONES AS ANGIOTENSIN II RECEPTOR ANTAGONISTS[†]

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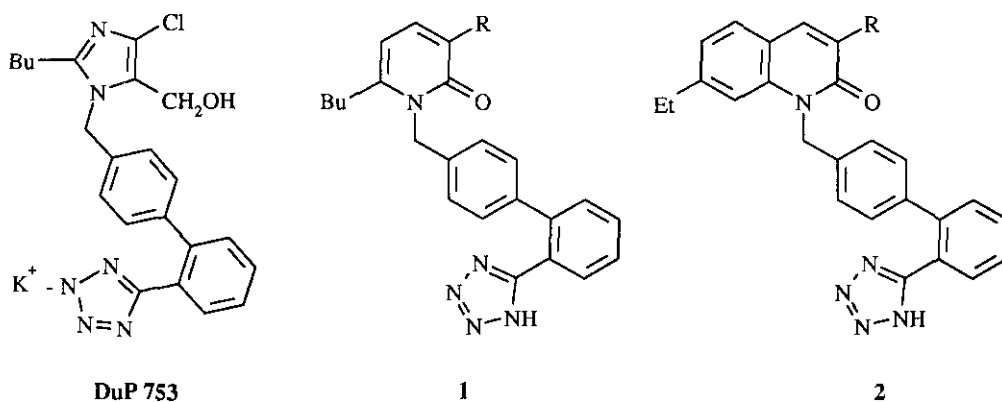
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Abstract - A number of biphenyl substituted 1,2-dihydroquinolin-2-ones were synthesized by regiospecific alkylation of the corresponding 1H-derivatives. Again, these precursors were prepared in three steps by acetoacetylation of anilines, regio-specific C-alkylation of the resulting β -ketoanilides and subsequent condensation to the quinolinones. One of the target compounds, 2-[7-ethyl-4-methyl-2-oxo-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-3-yl]-N,N-dimethylacetamide (**10e**), is a potent angiotensin II receptor antagonist.

The tetrasubstituted imidazole losartan (**DuP 753**) is the prototype of potent, selective and orally active non-peptide angiotensin II receptor antagonists.¹ This compound is currently in clinical trials as an agent for the treatment of hypertension.² The alkyl chain and the biphenyltetrazole attached to the imidazole ring are the key structural features within this class of drugs. The imidazole moiety, however, can be replaced by a number of other heterocycles such as benzimidazoles,³ imidazopyridines,⁴ 1,2,4-triazoles⁵ or 4-aminopyridines.⁶ As part of a survey to replace the potential imidazole moiety with other heterocyclic groups, we synthesized 3-substituted pyridones (**1**),⁷ which were found to be potent antagonists of angiotensin II. We were also interested in making rigid analogues of **1** by forming a ring between the pyridone nucleus and the butyl chain to provide quinolinones (**2**) with the alkyl chain attached to the 7-position. In this paper we report the syntheses and *in vitro* properties of selected 3,4,7-trisubstituted 1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydro-

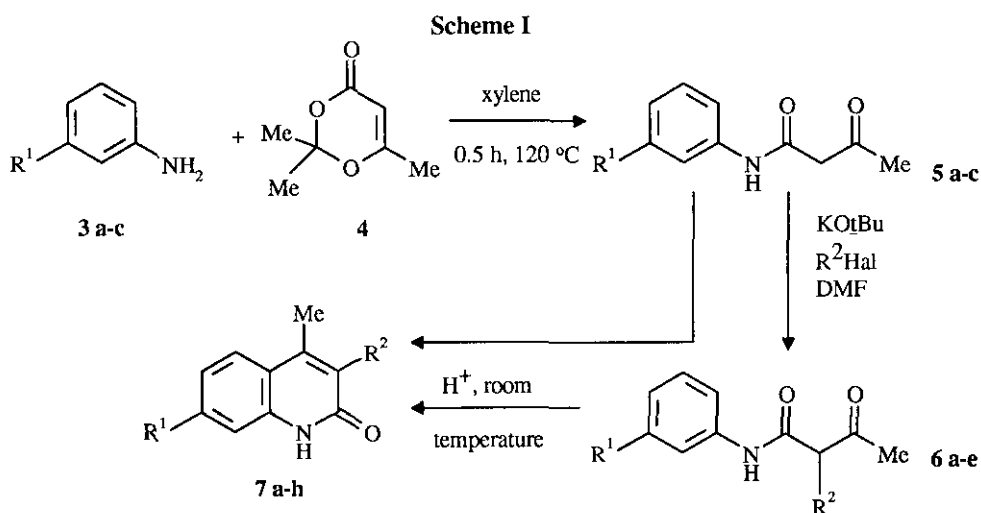
[†] Dedicated to Dr. Arnold Brossi on the occasion of his 70th birthday.

droquinolin-2-ones as angiotensin II antagonists.



Two methods have been established for the preparation of a wide range of 3,7-disubstituted 1,2-dihydroquinolin-2-ones: Condensation of malonates with anilines leading to 4-hydroxy derivatives⁸ and condensation of anilines with ethyl 2-alkylacetoacetates giving rise to 4-methyl derivatives.⁹ On account of broad variations in the 3-position we sought for a reliable method for the preparation of this ring system. We utilized the previously reported Knorr cyclization of an acetoacetanilide derivative obtained from *o*-anisidine and diketene.¹⁰ Instead of diketene the commercially available 2,2,6-trimethyl-4H-1,3-dioxin-4-one (**4**) (dioxinone) was used.¹¹

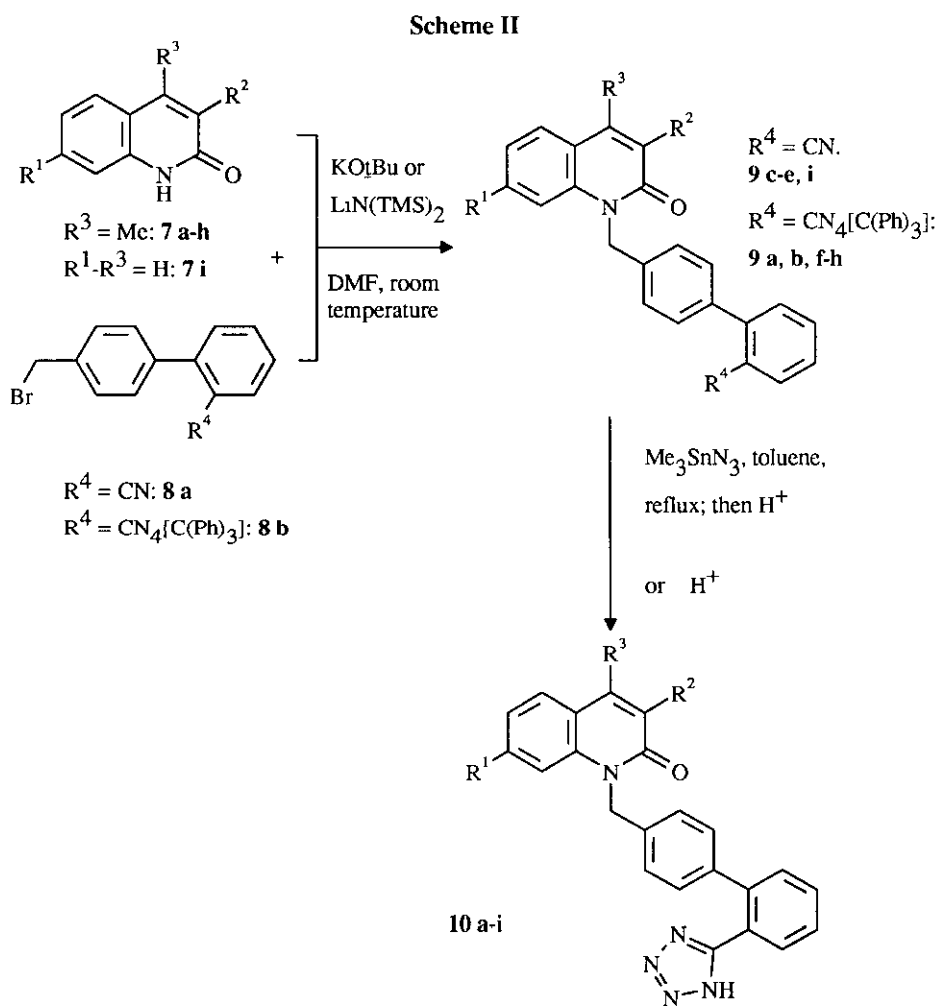
The synthesis of 3,7-disubstituted 1,2-dihydroquinolin-2-one intermediates was carried out according to Scheme I.



Reaction of anilines (**3a-c**) with dioxinone (**4**) led smoothly to the β -ketoanilides (**5a-c**). Treatment of **5a-c**

with potassium *tert*-butoxide and alkyl halides afforded the corresponding 2-substituted anilides (**6a-e**) in reasonable yields. However, these compounds are accompanied by minor amounts of 2,2-disubstituted analogues, which could be easily separated and isolated in pure form by column chromatography. Acid catalyzed cyclisation of **5a-c** and **6a-e** in sulfuric acid gave 4-methylquinolin-2-ones (**7a-h**). Ring closure in **7a-g** occurred only at para position to the alkyl substituent of the phenyl moiety. In spite of the relatively mild reaction conditions the amounts of the desired products dropped to 40% in case of the substrates with acid-labile functional groups.

Scheme II describes the sequence of reactions which led to the preparation of the target molecules (**10a-i**).

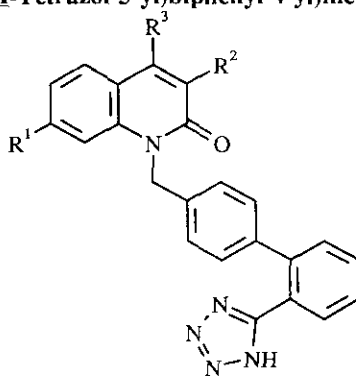


Alkylation of quinolinones (**7a-i**) with biphenylmethyl bromide (**8a**)¹² or (**8b**)¹² in the presence of potassium

comparison. Results shown in Table I indicate that receptor affinity increase with alkylsubstitution at 3-, 4- and 7- positions of the quinolinone ring. However, replacement of the 3-methyl group (R^2) in **10a** with benzyl derivatives, **10b** and **10c** led to a significant drop in binding affinity. Introduction of carbonylmethyl functionalities at this position unexpectedly improved the biological activity. The most potent tetrazole analogue (**10e**) in this series displayed functional antagonism equal to **DuP 753**. We believe that this is the result of a specific receptor interaction of the amide moiety with a proton donor on one receptor side.

Table I:

Biological Activity of 1-[(2'-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-ones



compound	R^1	R^2	R^3	binding; IC_{50}^a (nM)	antagonism; IC_{50}^b (nM)
10i	H	H	H	23,000.0	nt
10h	H	H	CH ₃	7,500.0	nt
10g	CH ₃	H	CH ₃	360.0	nt
10f	CH ₃ CH ₂	H	CH ₃	280.0	40.0
10a	CH ₃ CH ₂	CH ₃	CH ₃	80.0	nt
10b	CH ₃ CH ₂	CH ₂ Ph	CH ₃	110.0	nt
10c	CH ₃ CH ₂	CH ₂ Ph(4-NO ₂)	CH ₃	300.0	nt
10d	CH ₃ CH ₂	CH ₂ CO ₂ CH ₃	CH ₃	60.0	100.0
10e	CH ₃ CH ₂	CH ₂ CON(CH ₃) ₂	CH ₃	10.0	3.0
DuP 753	-----	-----	-----	8.2	3.0

a = rat adrenal cortex, b = rabbit aorta, nt = not tested

In conclusion, we have described the regioselective synthesis of tetrasubstituted 1,2-dihydroquinolin-2-ones, leading to novel and potent angiotensin II antagonists.

EXPERIMENTAL

General. Melting points were determined with a Mettler FP 62 melting point apparatus and are uncorrected. Ir, nmr, and mass spectra (ms) were recorded on a Bruker 85 IFS 48 IR spectrophotometer, a Bruker AC 200, WM 250, or AM 500 (TMS as an internal standard), and a Fisons (formerly Vacuum Generator) VG 70-70E (electron-impact: ei) or 70-250SE (fast atom bombardement: fab) at 70 eV, respectively. Microanalyses were obtained with a Perkin-Elmer 240B CHN analyzer. Flash chromatography was carried out on E. Merck (Darmstadt, Germany) Kieselgel 60 silica gel (240-400 mesh). Thin-layer chromatography (tlc) was carried out on precoated silica gel 60 F₂₅₄ plates with a layer thickness of 0.25 mm from E. Merck. Visualization was done with uv and I₂. Yields are not optimized. Radioligand binding studies were performed using rat adrenal cortical membranes prepared as described by Chiu *et al.*¹⁶ Binding experiments were performed essentially as described¹⁶ using [¹²⁵I] Tyr⁴ angiotensin II as the radioligand. Contractile responses in rabbit aorta were determined as described elsewhere.¹⁷

General procedure for preparation of 3-oxobutyramides. **N-(3-Ethylphenyl)-3-oxobutyramide (5a).** Freshly distilled 2,2,6-trimethyl-4H-1,3-dioxin-4-one (**4**) (18.0 g, 130 mmol) was added to a mixture of 3-ethylaniline (15.0 g, 130 mmol) in dry xylene (75 ml, isomeric mixture) at 120 °C. The resulting mixture was stirred at 120 °C for 0.5 h. During reaction evolution of acetone became apparent. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate - hexane (9:1), to give **5a** as an oil, 25.0 g (96%); nmr (δ, ppm, DMSO-d₆): 1.16 (3H, t, J = 7.6 Hz), 1.91 (3H, s), 2.21 (3H, s), 2.57 (2H, q, J = 7.6 Hz), 3.53 (2H, s), 6.90 (1H, td, J = 1.2 and 6.3 Hz), 7.20 (1H, t, J = 6.4 Hz), 7.35-7.45 (2H, m), 9.98 (1H, br s); ms (ei), m/z = 205 (M⁺). Anal. Calcd for C₁₂H₁₅NO₂ · 0.1 H₂O: C, 69.65; H, 7.40; N, 6.76. Found: C, 69.80; H, 7.50; N, 6.70.

N-(3-Methylphenyl)-3-oxobutyramide (5b). This compound was first described by Ewins *et al.*¹⁸

N-Phenyl-3-oxobutyramide (5c). This compound was first described by Knorr.¹⁹

General procedure for alkylation of 3-oxobutyramides. **N-(3-Ethylphenyl)-2-methyl-3-oxobutyramide (6a).** To a mixture of **5a** (3.0 g, 14.6 mmol) and potassium *tert*-butoxide (1.6 g, 14.6 mmol) in dimethylformamide (100 ml) at ambient temperature under nitrogen was added methyl iodide (0.9 ml, 14.6

mmol). The resulting mixture was stirred for 5 h, then poured into brine and extracted with ethyl acetate. The extract was dried and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate - hexane (3:7), to give **6a** as white solids, 1.80 g (56%), mp 56-57 °C; nmr (δ , ppm, DMSO- d_6): 1.17 (3H, t, $J = 7.6$ Hz), 1.23 (3H, d, $J = 7.1$ Hz), 2.17 (3H, s), 2.58 (2H, q, $J = 7.6$ Hz), 3.65 (1H, dd, $J = 7.0$ and 7.0 Hz), 6.92 (1H, td, $J = 1.3$ and 7.6 Hz), 7.21 (1H, t, $J = 7.8$ Hz), 7.37-7.47 (2H, m), 10.12 (1H, br s); ms (ei), $m/z = 219$ (M^+). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.20; H, 7.90; N, 6.40.

2-Benzyl-N-(3-ethylphenyl)-3-oxobutyramide (6b). This compound was obtained as white solids (48%), mp 71-72 °C; nmr (δ , ppm, DMSO- d_6): 1.15 (3H, t, $J = 7.6$ Hz), 2.19 (3H, s), 2.55 (2H, q, $J = 7.6$ Hz), 3.08 (2H, d, $J = 7.4$ Hz), 3.95 (1H, t, $J = 7.4$ Hz), 6.90 (1H, td, $J = 1.4$ and 7.5 Hz), 7.11-7.33 (7H, m), 7.36 (1H, d, $J = 1.3$ Hz), 10.10 (1H, br s); ms (ei), $m/z = 295$ (M^+). Anal. Calcd for $C_{19}H_{21}NO_2 \cdot 0.1 H_2O$: C, 76.82; H, 7.19; N, 4.71. Found: C, 76.90; H, 7.10; N, 4.90.

N-(3-Ethylphenyl)-2-(4-nitrobenzyl)-3-oxobutyramide (6c). This compound was obtained as white solids (75%), mp 161-162 °C; nmr (δ , ppm, DMSO- d_6): 1.15 (3H, t, $J = 7.6$ Hz), 2.22 (3H, s), 2.55 (2H, q, $J = 7.6$ Hz), 3.21 (2H, d, $J = 7.4$ Hz), 4.04 (1H, t, $J = 7.4$ Hz), 6.91 (1H, d, $J = 7.6$ Hz), 7.19 (1H, d, $J = 7.6$ Hz), 7.29-7.35 (2H, m), 7.51 (2H, d, $J = 8.8$ Hz), 8.13 (2H, d, $J = 8.8$ Hz), 10.18 (1H, br s); ms (fab), $m/z = 341$ (M^+). Anal. Calcd for $C_{19}H_{20}N_2O_4 \cdot 0.25 H_2O$: C, 66.21; H, 5.99; N, 8.13. Found: C, 66.20; H, 6.00; N, 8.10.

Methyl 3-[N-(3-ethylphenyl)carbamoyl]-4-oxopentanoate (6d). This compound was obtained as an oil (47%); nmr (δ , ppm, DMSO- d_6): 1.17 (3H, t, $J = 7.6$ Hz), 2.23 (3H, s), 2.58 (2H, q, $J = 7.6$ Hz), 2.78 (2H, dd, $J = 7.1$ and -17.1 Hz), 2.88 (2H, dd, $J = 7.2$ and -17.1 Hz), 3.60 (3H, s), 4.09 (1H, t, $J = 7.2$ Hz), 6.92 (1H, td, $J = 1.3$ and 7.6 Hz), 7.22 (1H, t, $J = 7.6$ Hz), 7.36-7.48 (2H, m), 10.20 (1H, br s); ms (ei), $m/z = 277$ (M^+). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.20; H, 7.00; N, 5.20.

2-Acetyl-N-(3-ethylphenyl)-N',N'-dimethylsuccinamide (6e). This compound was obtained as an oil (49%); nmr (δ , ppm, DMSO- d_6): 1.16 (3H, t, $J = 7.6$ Hz), 2.21 (3H, s), 2.57 (2H, q, $J = 7.6$ Hz), 2.76 (2H, dd, $J = 6.6$ and -17.4 Hz), 2.88 (2H, dd, $J = 6.7$ and -17.4 Hz), 2.80 (3H, s), 2.99 (3H, s), 4.09 (1H, t, $J = 6.7$ Hz), 6.90 (1H, d, $J = 7.7$ Hz), 7.20 (1H, d, $J = 7.8$ Hz), 7.35-7.48 (2H, m), 10.24 (1H, br s); ms (ei), $m/z = 290$ (M^+). Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.19; H, 7.64; N, 9.65. Found: C, 66.30; H, 7.80; N, 9.60.

General procedure for preparation of 1,2-dihydroquinolin-2-ones. **7-Ethyl-3,4-dimethyl-1,2-dihy-**

droquinolin-2-one (7a). A solution of **6a** (1.0 g, 4.6 mmol) in concentrated sulfuric acid (5.0 ml) was stirred at ambient temperature for 1 h. The reaction mixture was poured into ice water, and the resultant precipitates were filtered, washed with water, dried and recrystallized from ethyl acetate - hexane (1:1) to give **7a** as white solids, 0.85 g (94%), mp 207-208 °C; nmr (δ , ppm, DMSO- d_6): 1.20 (3H, t, $J = 7.6$ Hz), 2.10 (3H, s), 2.38 (3H, s), 2.65 (2H, q, $J = 7.6$ Hz), 7.03 (1H, dd, $J = 1.8$ and 8.3 Hz), 7.10 (1H, d, $J = 1.8$ Hz), 7.63 (1H, d, $J = 8.3$ Hz), 11.52 (1H, br s); ms (ei), $m/z = 201$ (M^+). Anal. Calcd for $C_{13}H_{15}NO \cdot 0.1 H_2O$: C, 76.94; H, 7.54; N, 6.90. Found: C, 76.80; H, 7.60; N, 7.20.

3-Benzyl-7-ethyl-4-methyl-1,2-dihydroquinolin-2-one (7b). This compound was prepared in 20% H_2SO_4 (20 ml) as described above and obtained as white solids (54%), mp 259-260 °C; nmr (δ , ppm, DMSO- d_6): 1.20 (3H, t, $J = 7.6$ Hz), 2.39 (3H, s), 2.66 (2H, q, $J = 7.6$ Hz), 4.02 (2H, s), 7.05 (1H, dd, $J = 1.8$ and 8.4 Hz), 7.09-7.33 (6H, m), 7.64 (1H, d, $J = 8.3$ Hz), 11.68 (1H, br s); ms (ei), $m/z = 277$ (M^+). Anal. Calcd for $C_{19}H_{19}NO \cdot 0.2 H_2O$: C, 80.28; H, 6.95; N, 4.99. Found: C, 80.40; H, 6.90; N, 4.80.

7-Ethyl-4-methyl-3-(4-nitrobenzyl)-1,2-dihydroquinolin-2-one (7c). This compound was obtained as white solids (58%), mp 280-281 °C; nmr (δ , ppm, DMSO- d_6): 1.20 (3H, t, $J = 7.6$ Hz), 2.41 (3H, s), 2.66 (2H, q, $J = 7.6$ Hz), 4.16 (2H, s), 7.07 (1H, dd, $J = 1.5$ and 8.2 Hz), 7.14 (1H, s), 7.48 (2H, d, $J = 8.7$ Hz), 7.68 (1H, d, $J = 8.2$ Hz), 8.12 (2H, d, $J = 8.7$ Hz), 11.71 (1H, br s); ms (ei), $m/z = 322$ (M^+). Anal. Calcd for $C_{19}H_{18}N_2O_3 \cdot 0.1 H_2O$: C, 70.42; H, 5.66; N, 8.64. Found: C, 70.40; H, 5.72; N, 8.70.

Methyl 2-(7-ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-3-yl)acetate (7d). This compound was obtained as white solids (40%), mp 209-210 °C; nmr (δ , ppm, DMSO- d_6): 1.21 (3H, t, $J = 7.5$ Hz), 2.37 (3H, s), 2.67 (2H, q, $J = 7.5$ Hz), 3.60 (3H, s), 3.71 (2H, s), 7.07 (1H, dd, $J = 1.8$ and 8.3 Hz), 7.13 (1H, d, $J = 1.6$ Hz), 7.70 (1H, d, $J = 8.3$ Hz), 11.53 (1H, br s); ms (ei), $m/z = 259$ (M^+). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.60; H, 6.87; N, 5.30.

2-(7-Ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-*N,N*-dimethylacetamide (7e). This compound was obtained as white solids (44%), mp 232-233 °C; nmr (δ , ppm, DMSO- d_6): 1.20 (3H, t, $J = 7.5$ Hz), 2.30 (3H, s), 2.67 (2H, q, $J = 7.5$ Hz), 2.83 (3H, s), 3.11 (3H, s), 3.70 (2H, s), 7.05 (1H, dd, $J = 1.8$ and 8.3 Hz), 7.11 (1H, d, $J = 1.7$ Hz), 7.65 (1H, d, $J = 8.3$ Hz), 11.51 (1H, br s); ms (ei), $m/z = 272$ (M^+). Anal. Calcd for $C_{16}H_{20}N_2O_2 \cdot 0.2 H_2O$: C, 69.69; H, 7.45; N, 10.16. Found: C, 69.80; H, 7.40; N, 10.20.

7-Ethyl-4-methyl-1,2-dihydroquinolin-2-one (7f). This compound was obtained as white solids (92%), mp 179-180 °C; nmr (δ , ppm, DMSO- d_6): 1.20 (3H, t, $J = 7.5$ Hz), 2.40 (3H, d, $J = 1.2$ Hz), 2.67 (2H, q, $J = 7.5$

Hz), 6.31 (1H, d, $J = 1.3$ Hz), 7.05 (1H, dd, $J = 1.8$ and 8.2 Hz), 7.12 (1H, d, $J = 1.7$ Hz), 7.61 (1H, d, $J = 8.2$ Hz), 11.48 (1H, br s); ms (ei), $m/z = 187$ (M^+). Anal. Calcd for $C_{12}H_{13}NO \cdot 0.4 H_2O$: C, 74.28; H, 7.15; N, 7.22. Found: C, 74.40; H, 7.17; N, 7.10.

4,7-Dimethyl-1,2-dihydroquinolin-2-one (7g). This compound was first described by Tikotikar *et al.*²⁰

4-Methyl-1,2-dihydroquinolin-2-one (7h). This compound was first described by Ochiai *et al.*²¹

General procedure for alkylation of 1,2-dihydroquinolin-2-ones. **7-Ethyl-4-methyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (9f).** A mixture of **7f** (2.0 g, 10.7 mmol), biphenylmethyl bromide (**8b**) (7.2 g, 12.8 mmol) and potassium *tert*-butoxide (1.4 g, 12.8 mmol) in dimethylformamide (150 ml) was stirred at ambient temperature for 2 h, the reaction mixture was poured into water. The resultant precipitates were filtered, washed with water and dried. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate - hexane (1:1), to give **9f** as white solids, 4.3 g (61%), mp 164-165 °C; nmr (δ , ppm, DMSO- d_6): 1.03 (3H, t, $J = 7.5$ Hz), 2.47 (3H, d, $J = 1.2$ Hz), 2.50 (2H, q, $J = 7.6$ Hz), 5.50 (2H, br s), 6.59 (1H, d, $J = 1.3$ Hz), 6.84-7.19 (12H, m), 7.26-7.76 (14H, m); ms (fab), $m/z = 664$ (M^+). Anal. Calcd for $C_{45}H_{37}N_5O \cdot 0.3 H_2O$: C, 80.78; H, 5.67; N, 10.47. Found: C, 80.80; H, 5.83; N, 10.60.

7-Ethyl-3,4-dimethyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (9a). This compound was obtained as white solids (64%), mp 108-109 °C; nmr (δ , ppm, DMSO- d_6): 1.06 (3H, t, $J = 7.6$ Hz), 2.25 (3H, s), 2.47 (3H, s), 2.50 (2H, q, $J = 7.6$ Hz), 5.54 (2H, br s), 6.87-6.90 (6H, m), 7.02 (2H, d, $J = 8.2$ Hz), 7.08 (1H, d, $J = 8.0$ Hz), 7.11 (2H, d, $J = 8.2$ Hz), 7.15 (1H, s), 7.30-7.38 (9H, m), 7.41 (1H, d, $J = 7.5$ Hz), 7.52 (1H, td, $J = 0.9$ and 7.5 Hz), 7.59 (1H, td, $J = 1.2$ and 7.7 Hz), 7.74 (1H, dd, $J = 8.2$ and 0.9 Hz), 7.77 (1H, d, $J = 8.0$ Hz); ms (ei), $m/z = 678$ (M^+). Anal. Calcd for $C_{46}H_{39}N_5O$: C, 81.51; H, 5.80; N, 10.33. Found: C, 81.40; H, 6.00; N, 10.10.

3-Benzyl-7-ethyl-4-methyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (9b). This compound was obtained with 1.0 M LiN(TMS)₂ in THF instead of KO_tBu as white solids (53%), mp 154-155 °C; nmr (δ , ppm, DMSO- d_6): 1.13 (3H, t, $J = 7.5$ Hz), 2.48 (3H, s), 2.51 (2H, q, $J = 7.5$ Hz), 4.17 (2H, s), 5.56 (2H, br s), 6.86-6.89 (6H, m), 7.02 (2H, d, $J = 8.2$ Hz), 7.07-7.18 (5H, M), 7.24-7.26 (4H, m), 7.28-7.35 (9H, m), 7.41 (1H, dd, $J = 0.8$ and 7.5 Hz), 7.52 (1H, td, $J = 1.3$ and 7.8 Hz), 7.60 (1H, td, $J = 1.2$ and 7.4 Hz), 7.74 (1H, dd, $J = 1.2$ and 7.8 Hz), 7.78 (1H, d, $J = 8.3$ Hz); ms (fab), $m/z = 754$ (M^+). Anal. Calcd for $C_{52}H_{43}N_5O \cdot 0.5H_2O$: C, 82.18; H, 5.82; N, 9.18. Found: C,

82.20; H, 6.10; N, 8.90.

4,7-Dimethyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (9g). This compound was obtained as white solids (57%), mp 204-205 °C; nmr (δ , ppm, DMSO- d_6): 2.19 (3H, s), 2.49 (3H, s), 5.46 (2H, br s), 6.57 (1H, s), 6.85-6.88 (6H, m), 7.01-7.10 (5H, m), 7.15 (1H, s), 7.29-7.37 (9H, m), 7.42 (1H, dd, $J = 0.8$ and 7.9 Hz), 7.52 (1H, td, $J = 1.1$ and 7.5 Hz), 7.59 (1H, td, $J = 1.3$ and 7.5 Hz), 7.69 (1H, d, $J = 8.2$ Hz), 7.74 (1H, dd, $J = 1.2$ and 7.8 Hz); ms (fab), $m/z = 650$ (M^+). Anal. Calcd for $C_{44}H_{35}N_5O$: C, 81.33; H, 5.43; N, 10.78. Found: C, 81.20; H, 4.90; N, 10.40.

4-Methyl-1-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (9h). This compound was obtained as white solids (61%), mp 191-192 °C; nmr (δ , ppm, DMSO- d_6): 2.49 (3H, s), 5.46 (2H, br s), 6.67 (1H, s), 6.84-6.86 (5H, m), 7.01 (2H, d, $J = 8.3$ Hz), 7.07 (2H, d, $J = 8.3$ Hz), 7.19-7.37 (12H, m), 7.41 (1H, d, $J = 7.8$ Hz), 7.52 (1H, td, $J = 1.0$ and 7.5 Hz), 7.59 (1H, td, $J = 1.2$ and 7.4 Hz), 7.76 (1H, dd, $J = 1.0$ and 7.4 Hz), 7.81 (1H, dd, $J = 1.1$ and 7.9 Hz); ms (ei), $m/z = 636$ (M^+). Anal. Calcd for $C_{43}H_{33}N_5O$: C, 81.24; H, 5.23; N, 11.02. Found: C, 81.50; H, 5.30; N, 11.30.

The following compounds were prepared with biphenylmethyl bromide (8a) in an analogous manner.

2-[4-((7-Ethyl-4-methyl-3-(4-nitrobenzyl)-2-oxo-1,2-dihydroquinolin-1-yl)methyl)phenyl]benzonitrile (9c). This compound was obtained as white solids (44%), mp 170-171 °C; nmr (δ , ppm, DMSO- d_6): 1.14 (3H, t, $J = 7.5$ Hz), 2.51 (3H, s), 2.66 (2H, q, $J = 7.5$ Hz), 4.31 (3H, s), 5.70 (3H, br s), 7.15 (1H, dd, $J = 1.4$ and 8.3 Hz), 7.33-7.38 (2H, m), 7.41 (1H, s), 7.51-7.61 (6H, m), 7.74 (1H, dd, $J = 1.5$ and 7.6 Hz), 7.83 (1H, d, $J = 8.2$ Hz), 7.91 (1H, d, $J = 7.9$ Hz), 8.15 (2H, d, $J = 8.8$ Hz); ms (fab), $m/z = 514$ (M^+). Anal. Calcd for $C_{33}H_{27}N_3O_3$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.00; H, 5.44; N, 7.90.

Methyl 2-[1-((2'-cyanobiphenyl-4-yl)methyl)-7-ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-3-yl]acetate (9d). This compound was obtained as white solids (48%), mp 115-116 °C; nmr (δ , ppm, DMSO- d_6): 1.13 (3H, t, $J = 7.6$ Hz), 2.46 (3H, s), 2.65 (2H, q, $J = 7.6$ Hz), 3.63 (3H, s), 3.86 (2H, s), 5.65 (2H, br s), 7.14 (1H, dd, $J = 0.9$ and 8.4 Hz), 7.32 (1H, s), 7.37 (2H, d, $J = 8.2$ Hz), 7.47-7.62 (4H, m), 7.75 (1H, td, $J = 0.9$ and 7.2 Hz), 7.81 (1H, d, $J = 8.2$ Hz), 7.91 (1H, dd, $J = 0.9$ and 7.8 Hz); ms (fab), $m/z = 451$ (M^+). Anal. Calcd for $C_{29}H_{26}N_2O_3 \cdot 0.2 H_2O$: C, 76.72; H, 5.86; N, 6.17. Found: C, 76.70; H, 5.90; N, 6.10.

2-[1-((2'-Cyanobiphenyl-4-yl)methyl)-7-ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-3-yl]-*N,N*-dimethylacetamide (9e). This compound was obtained as white solids (46%), mp 189-190 °C; nmr (δ , ppm, DMSO- d_6): 1.13 (3H, t, $J = 7.6$ Hz), 2.39 (3H, s), 2.62 (2H, q, $J = 7.6$ Hz), 2.85 (3H, s), 3.15 (3H, s), 3.83 (2H, s),

5.63 (2H, br s), 7.14 (1H, dd, $J = 1.0$ and 8.4 Hz), 7.30 (1H, s), 7.36 (2H, d, $J = 8.3$ Hz), 7.51-7.59 (4H, m), 7.76 (1H, td, $J = 1.1$ and 7.8 Hz), 7.79 (1H, d, $J = 8.3$ Hz), 7.91 (1H, dd, $J = 0.8$ and 7.8 Hz); ms (ei), $m/z = 464$ (M^+). Anal. Calcd for $C_{30}H_{29}N_3O_2$: C, 77.73; H, 6.31; N, 9.06. Found: C, 77.70; H, 6.40; N, 9.20.

2-[4-((2-Oxo-1,2-dihydroquinolin-1-yl)methyl)phenyl]benzonitrile (9i). This compound was obtained from 2-hydroxyquinoline (7i) as white solids (52%), mp 175-176 °C; nmr (δ , ppm, DMSO- d_6): 5.61 (2H, br s), 6.81 (1H, d, $J = 9.4$ Hz), 7.16-7.78 (13H, m); ms (ei), $m/z = 336$ (M^+). Anal. Calcd for $C_{23}H_{16}N_2O \cdot 0.5 H_2O$: C, 80.04; H, 4.96; N, 8.12. Found: C, 79.90; H, 5.10; N, 8.00.

General procedure for preparation of tetrazoles. Methyl 2-[7-ethyl-4-methyl-2-oxo-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-3-yl]acetate (10d). Compound (9d) (0.8 g, 1.7 mmol) was allowed to reflux with trimethyltin azide (1.7 g, 8.5 mmol) in toluene (25 ml). The reaction mixture was stirred for 30 h and concentrated *in vacuo* to an oil. The residue was taken up in ice-cold, dry methanol (50 ml) saturated with HCl gas. The resulting mixture was stirred for 10 min before it was concentrated *in vacuo*. Flash chromatography (10% methanol in ethyl acetate as eluent) and recrystallisation from ethanol provided 10d as white solids, 0.53 g (65%), mp 215-216 °C; nmr (δ , ppm, DMSO- d_6): 1.13 (3H, t, $J = 7.5$ Hz), 2.44 (3H, s), 2.65 (2H, q, $J = 7.5$ Hz), 3.62 (3H, s), 3.82 (2H, s), 5.54 (2H, br s), 7.00-7.25 (6H, m), 7.46-7.68 (4H, m), 7.80 (1H, d, $J = 8.3$ Hz); ms (fab), $m/z = 494$ (M^+). Anal. Calcd for $C_{29}H_{27}N_5O_3 \cdot 0.6 H_2O$: C, 69.08; H, 5.63; N, 13.89. Found: C, 69.10; H, 5.53; N, 13.80.

7-Ethyl-4-methyl-3-(4-nitrobenzyl)-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10c) This compound was obtained as white solids (81%), mp 228-229 °C; nmr (δ , ppm, DMSO- d_6): 1.12 (3H, t, $J = 7.5$ Hz), 2.48 (3H, s), 2.64 (2H, q, $J = 7.5$ Hz), 4.28 (2H, s), 5.57 (2H, br s), 7.04 (2H, d, $J = 8.3$ Hz), 7.13 (1H, dd, $J = 0.9$ and 8.3 Hz), 7.16 (2H, d, $J = 8.3$ Hz), 7.24 (1H, s), 7.48-7.57 (4H, m), 7.62-7.67 (2H, m), 7.79 (1H, d, $J = 8.3$ Hz), 8.14 (2H, d, $J = 8.8$ Hz); ms (fab), $m/z = 557$ (M^+). Anal. Calcd for $C_{33}H_{28}N_6O_3$: C, 71.21; H, 5.07; N, 15.10. Found: C, 71.30; H, 5.15; N, 15.10.

2-[7-Ethyl-4-methyl-2-oxo-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-3-yl]-N,N-dimethylacetamide (10e). This compound was obtained as white solids (55%), mp 225-226 °C; nmr (δ , ppm, DMSO- d_6): 1.13 (3H, t, $J = 7.6$ Hz), 2.38 (3H, s), 2.65 (2H, q, $J = 7.6$ Hz), 2.85 (3H, s), 3.15 (3H, s), 3.82 (3H, s), 5.53 (2H, br s), 7.03 (2H, d, $J = 8.2$ Hz), 7.13 (1H, dd, $J = 0.9$ and 8.4 Hz), 7.16 (2H, d, $J = 8.2$ Hz), 7.22 (1H, s), 7.50 (1H, d, $J = 7.8$ Hz), 7.55 (1H, td, $J = 0.9$ and 8.2 Hz), 7.61-7.66 (2H, m), 7.77 (1H, d, $J = 8.3$ Hz); ms (fab), $m/z = 507$ (M^+). Anal. Calcd for $C_{30}H_{30}N_6O_2 \cdot 0.2 H_2O$: C, 70.64; H, 6.01; N,

16.48. Found: C, 70.60; H, 6.10; N, 16.50.

1-[(2'-(1H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10i) This compound was obtained as white solids (72%), mp 265-266 °C; nmr (δ , ppm, DMSO- d_6): 5.52 (2H, br s), 6.73 (1H, d, $J = 9.5$ Hz), 7.04 (2H, d, $J = 8.2$ Hz), 7.15 (2H, d, $J = 8.2$ Hz), 7.25 (1H, t, $J = 7.5$ Hz), 7.40 (1H, d, $J = 8.6$ Hz), 7.50-7.58 (4H, m), 7.63-7.68 (2H, m), 7.76 (1H, dd, $J = 1.5$ and 7.5 Hz), 8.00 (1H, d, $J = 9.5$ Hz), 16.25 (1H, br s); ms (fab), $m/z = 381$ (M^+). Anal. Calcd for $C_{23}H_{17}N_5O \cdot 1.1 H_2O$: C, 69.21; H, 4.85; N, 17.54. Found: C, 69.20; H, 4.70; N, 17.54.

General procedure for deprotection of tetrazoles. **7-Ethyl-4-methyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2 dihydroquinolin-2-one (10f).** A mixture of **9f** (0.5 g, 0.75 mmol), formic acid (5 ml) and methanol (45 ml) was stirred at 50 °C for 2 h. The solution was concentrated *in vacuo* and the residue was triturated with methanol to give **10f** as white solids, 278 mg (88%), mp 260-261 °C; nmr (δ , ppm, DMSO- d_6): 1.11 (3H, t, $J = 7.5$ Hz), 2.45 (3H, d, $J = 1.1$ Hz), 2.64 (2H, q, $J = 7.5$ Hz), 5.50 (2H, br s), 6.56 (1H, d, $J = 1.2$ Hz), 7.00-7.23 (6H, m), 7.46-7.73 (5H, m), 16.60 (1H, br s); ms (ei), $m/z = 421$ (M^+). Anal. Calcd for $C_{26}H_{23}N_5O \cdot 0.1 H_2O$: C, 73.79; H, 5.52; N, 16.55. Found: C, 73.70; H, 5.62; N, 16.80.

7-Ethyl-3,4-dimethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10a). This compound was obtained as white solids (61%), mp 242-243 °C; nmr (δ , ppm, DMSO- d_6): 1.12 (3H, t, $J = 7.6$ Hz), 2.21 (3H, s), 2.43 (3H, s), 2.62 (2H, q, $J = 7.6$ Hz), 5.53 (2H, br s), 7.00-7.20 (6H, m), 7.46-7.70 (4H, m), 7.74 (1H, d, $J = 8.2$ Hz), 11.20 (1H, br s); ms (fab), $m/z = 436$ (M^+). Anal. Calcd for $C_{27}H_{25}N_5O$: C, 74.46; H, 5.79; N, 16.08. Found: C, 74.70; H, 5.60; N, 16.00.

3-Benzyl-7-ethyl-4-methyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10b). This compound was obtained as white solids (72%), mp 137-138 °C; nmr (δ , ppm, DMSO- d_6): 1.13 (3H, t, $J = 7.6$ Hz), 2.46 (3H, s), 2.64 (2H, q, $J = 7.6$ Hz), 4.15 (2H, s), 5.58 (2H, br s), 7.04 (2H, d, $J = 8.3$ Hz), 7.12 (1H, dd, $J = 0.9$ and 8.4 Hz), 7.14-7.18 (3H, m), 7.22-7.28 (5H, m), 7.50 (1H, d, $J = 7.7$ Hz), 7.54 (1H, td, $J = 0.8$ and 7.3 Hz), 7.62-7.67 (2H, m), 7.77 (1H, d, $J = 8.3$ Hz); ms (fab), $m/z = 512$ (M^+). Anal. Calcd for $C_{33}H_{29}N_5O \cdot 0.3 H_2O$: C, 76.68; H, 5.77; N, 13.55. Found: C, 76.70; H, 5.80; N, 13.30.

4,7-Dimethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10g). This compound was obtained as white solids (73%), mp 279-280 °C; nmr (δ , ppm, DMSO- d_6): 2.35 (3H, s), 2.45 (3H, d, $J = 1.2$ Hz), 5.48 (2H, br s), 6.55 (1H, d, $J = 1.2$ Hz), 7.00-7.16 (5H, m), 7.22 (1H, s), 7.48-7.72

(5H, m), 16.20 (1H, br s); ms (fab), $m/z = 408$ (M^+). Anal. Calcd for $C_{25}H_{21}N_5O$: C, 73.69; H, 5.19; N, 17.19. Found: C, 73.40; H, 5.20; N, 17.20.

4-Methyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,2-dihydroquinolin-2-one (10h). This compound was obtained as white solids (70%), mp 280-281 °C; nmr (δ , ppm, DMSO- d_6): 2.48 (3H, d, $J = 1.3$ Hz), 5.50 (2H, br s), 6.63 (1H, d, $J = 1.3$ Hz), 7.00-7.15 (4H, m), 7.26 (1H, td, $J = 1.2$ and 8.2 Hz), 7.38 (1H, dd, $J = 1.2$ and 8.6 Hz), 7.47-7.70 (5H, m), 7.81 (1H, dd, $J = 1.6$ and 8.0 Hz), 16.25 (1H, br s); ms (fab), $m/z = 394$ (M^+). Anal. Calcd for $C_{24}H_{19}N_5O \cdot 0.3 H_2O$: C, 72.31; H, 4.97; N, 17.57. Found: C, 72.30; H, 4.80; N, 18.00.

2-Acetyl-N-(3-ethylphenyl)-5,5-dimethyl-4-oxocaproamide (11). This compound was obtained by the method described for **6a** as white solids (48%), mp 121-122 °C; nmr (δ , ppm, DMSO- d_6): 1.10 (9H, s), 1.17 (3H, t, $J = 7.5$ Hz), 2.21 (3H, s), 2.58 (2H, q, $J = 7.5$ Hz), 2.98 (2H, dd, $J = 6.4$ and -18.3 Hz), 3.17 (2H, dd, $J = 6.4$ and -18.3 Hz), 4.05 (1H, t, $J = 6.4$ Hz), 6.91 (1H, d, $J = 7.5$ Hz), 7.21 (1H, t, $J = 7.6$ Hz), 7.36-7.46 (2H, m), 10.24 (1H, s); ms (ei), $m/z = 303$ (M^+). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.30; H, 8.50; N, 4.70.

2-Cyanomethyl-N-(3-ethylphenyl)-3-oxobutyramide (12). This compound was obtained as an oil (41%), nmr (δ , ppm, DMSO- d_6): 1.18 (3H, t, $J = 7.6$ Hz), 2.24 (3H, s), 2.59 (2H, q, $J = 7.6$ Hz), 2.90 (2H, d, $J = 7.1$ Hz), 4.07 (1H, t, $J = 7.1$ Hz), 6.97 (1H, d, $J = 7.6$ Hz), 7.25 (1H, t, $J = 7.6$ Hz), 7.37-7.47 (2H, m), 10.52 (1H, br s); ms (ei), $m/z = 244$ (M^+). Anal. Calcd for $C_{14}H_{16}N_2O_2 \cdot 0.05 H_2O$: C, 68.59; H, 6.62; N, 11.43. Found: C, 68.50; H, 6.50; N, 11.40.

2-(7-Ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-3-yl)acetamide (13). This compound was obtained by the method described for **7a** as white solids (60%), mp 289-290 °C; nmr (δ , ppm, DMSO- d_6): 1.20 (3H, t, $J = 7.5$ Hz), 2.36 (3H, s), 2.66 (2H, q, $J = 7.5$ Hz), 3.50 (2H, s), 6.79 (1H, br s), 7.05 (1H, dd, $J = 1.8$ and 8.3 Hz), 7.11 (1H, d, $J = 1.7$ Hz), 7.20 (1H, br s), 7.66 (1H, d, $J = 8.3$ Hz), 11.52 (1H, br s); ms (ei), $m/z = 244$ (M^+). Anal. Calcd for $C_{14}H_{16}N_2O_2 \cdot 1.8 H_2O$: C, 60.81; H, 7.13; N, 10.13. Found: C, 60.90; H, 7.30; N, 10.10.

The following compound was prepared in an analogous manner. **5-tert-Butyl-N-(3-ethylphenyl)-2-methylfuran-3-carboxamide (14).** This compound was obtained as white solids (75%), mp 134-135 °C; nmr (δ , ppm, DMSO- d_6): 1.19 (3H, t, $J = 7.5$ Hz), 1.26 (9H, s), 2.51 (3H, s), 2.59 (2H, q, $J = 7.5$ Hz), 6.68 (1H, s), 6.91 (1H, d, $J = 7.6$ Hz), 7.21 (1H, t, $J = 7.8$ Hz), 7.53 (1H, d, $J = 7.9$ Hz), 7.56 (1H, s), 9.49 (1H, s); ms

(ei), $m/z = 285$ (M^+). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.60; H, 8.30; N, 4.80.

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