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Isoquinolone derivatives via a furan recyclization reaction

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Abstract—A new approach to the synthesis of isoquinolone derivatives has been developed. It is based on the protolytic recyclization of amides of 2-carboxybenzylfurans. It was shown that the reaction proceeds via formation of allylic alcohols of isoquinolone series, which under acidic conditions undergo isomerization into the corresponding ketones. A new condensed heterocyclic system of furo[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one has been synthesized.

1. Introduction

The development of new effective methods for the synthesis of the isoquinolone ring system is an important research area for synthetic as well as for medicinal chemistry. Considerable interest from the synthetic community to this class of heterocycles is stipulated by the fact that 1(2*H*)-isoquinolone skeleton constitutes the framework of large variety of plant alkaloids[1] and synthetic compounds with a wide range of biological activity.[2] Isoquinolones are also attractive from the synthetic point of view since they can be used as a starting material in the total synthesis of natural alkaloids.[3]

By now, sufficiently vast information about construction of isoquinolone skeleton has been accumulated.[4] Among a great number of synthetic approaches, our attention was attracted by the methods based on the spontaneous cyclization of amides of *ortho*-carboxybenzylcarbonyl compounds **A** formed during the reaction (Fig. 1).

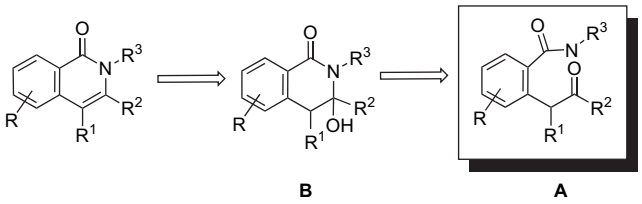

Figure 1. Retrosynthetic analysis of isoquinolone ring system synthesis from *ortho*-carboxybenzylcarbonyl compounds.

The methods of generation of intermediates **A** can be different. In particular, the syntheses of the isoquinolone framework via lithiation of *N*-substituted 2-alkylbenzamides and subsequent treatment with DMF or other *N*,*N*-disubstituted amides was disclosed in the literature.[5] As an intermediate product amidol **B** had been isolated. Its formation can be rationalized as the result of spontaneous intramolecular cyclization of compound **A**, which was registered by spectral methods in one case.[5c] The amidol **B** isolation confirms the intermediacy of compound **A** in the synthesis of isoquinolone derivatives upon treatment of primary or secondary *ortho*-halobenzamides with ketone enolates under UV irradiation.[6] It is obvious that the acidic hydrolysis of 2-(2-oxoalkyl)benzonitriles resulting in isoquinolone framework formation also proceeds via intermediate **A**.[7]

It is well known that furan ring can serve as a latent 1,4-dicarbonyl compound.[8] This prerequisite underlies our successfully developed general method of construction of benzannelated heterocyclic compounds via the acid-catalyzed recyclization of *ortho*-substituted benzylfurans serving as equivalents of *ortho*-substituted benzylcarbonyl compounds. Varying the *ortho*-substituent allowed us to obtain heterocycles such as benzofurans,[9] indoles,[10] isochromones,[11] and isochromenes[12] (Scheme 1).

In this article, we propose a new synthetic method leading to isoquinolone ring system that is based upon previously reported single example[13] and report in full details concerning the study of recyclization of amides of 2-carboxybenzylfurans into isoquinolone derivatives. The isolation of the corresponding allylic alcohols allowed us to specify the possible mechanism of the reaction.

Keywords: Furan; Recyclization; Isoquinolone.
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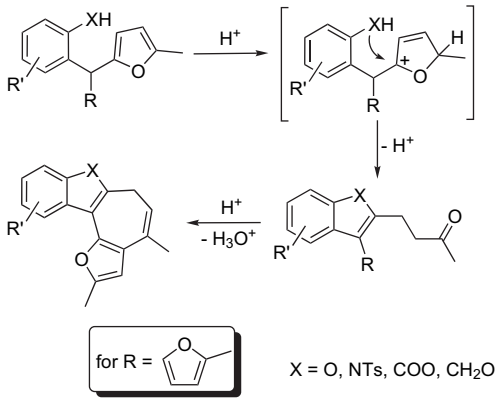
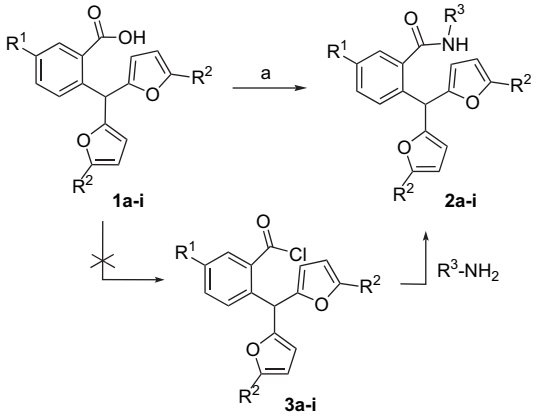


Scheme 1.



Scheme 2. (a) DCC, R^3–NH_2, CH_2Cl_2, rt.

2. Results and discussion

2.1. Synthesis of starting amides

The starting compounds for the synthesis of isoquinolone derivatives in our approach were 2-carboxybenzylfuran amides **2**, which were obtained from the readily available 2-carboxyaryldifurylmethanes **1**.[11c] The method of amide **2h** synthesis via refluxing acid **1h** in benzylamine[13] mentioned in preliminary communication is not suitable for the synthesis of amides derived from low-boiling amines. Therefore, we had tested other synthetic ways to the required amides.

It is known that acid chlorides are common precursors for the synthesis of the corresponding amides. However, we were not successful in obtaining acid chlorides **3**, probably as a consequence of furan ring susceptibility to acids and high mobility of the hydrogen atom attached to the methyne carbon atom. The interaction of acids **1** with PCl_5, $SOCl_2$, or oxalyl chloride[14] resulted only in the resinification of the reaction mixture. The same result was obtained when the α,α-dichloromethylmethyl ester was used.[15] The acceptable result was obtained only by generation of acid chloride in situ in the system of PPh_3–CCl_4 with the subsequent refluxing in the presence of amine.[16] However, the amide **2h** was obtained by this method in yield not exceeding 30%. Under such conditions many side-products were formed in the reaction mixture, which made difficulties in the chromatographical isolation of the desired product.

Finally, the amides **2** were obtained in satisfactory yields (30–36%) with the use of dicyclohexylcarbodiimide[17] (Scheme 2, Table 1). This method is optimal from the preparative point of view. Despite comparatively low yields the reaction proceeds clean enough and only two side-products were formed in the reaction mixture. The first one is dicyclohexylurea, which can be easily separated by filtration, and the second product is amide of dicyclohexylurea, which can be easily separated by column chromatography. The formation of the dicyclohexylurea amides causes low yields of amides.[18]

2.2. Recyclization reaction of amides

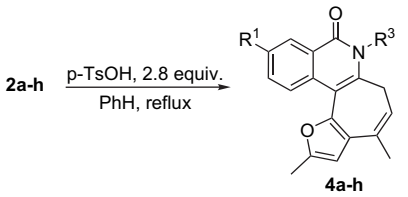
The amides **2** obtained were used in the further study of recyclization reaction. In our earlier work,[13] we reported that

Table 1. Synthesis of the amides **2a–i**

Entry	R^1	R^2	R^3	Product	Yield (%)
a	H	Me	H	**2a**	33
b	Cl	Me	Me	**2b**	35
c	Br	Me	Me	**2c**	32
d	H	Me	Me	**2d**	30
e	H	Me	Et	**2e**	36
f	H	Me	*i*-Pr	**2f**	34
g	H	Me	*t*-Bu	**2g**	32
h	H	Me	Bn	**2h**	35
i	H	*t*-Bu	Me	**2i**	33
j	Br	*t*-Bu	Me	**2j**	34

the isoquinolone derivative **4h** was obtained upon treatment of **2h** with boiling ethanol saturated with hydrogen chloride. However, further study had demonstrated that these conditions were not optimal. In many cases the reaction was accompanied with the formation of hardly separable side-products that eventually lead to the reduced yields of the desired products. We connected this fact with the possibility of hydrolysis or alcoholysis of amides under such conditions. The strong support for this assumption is an observation by TLC method of isocoumarine derivatives that were obtained earlier upon recyclization of acids **1** under the same conditions.[11c]

Attempting the search for the optimal conditions of this reaction, we have found that refluxing amides **2a–h** within 25 min in 16% solution of *p*-TsOH in benzene led to tetracyclic isoquinolones **4a–h** in moderate yields of 45–57% (Scheme 3, Table 2) that were fully characterized by spectral methods. For unambiguous proof of structure, X-ray analysis was performed for **4h** (Fig. 2).[19]



Scheme 3.

The exception is the amide **2g**, which did not give the corresponding isoquinolone **4g**, the fact that we explain by steric

Table 2. Synthesis of tetracyclic isoquinolones **4a–h**

Entry	R^1	R^3	Product	Yield (%)
a	H	H	**4a**	54
b	Cl	Me	**4b**	57
c	Br	Me	**4c**	57
d	H	Me	**4d**	55
e	H	Et	**4e**	55
f	H	*i*-Pr	**4f**	45
g	H	*t*-Bu	**4g**	0
h	H	Bn	**4h**	55

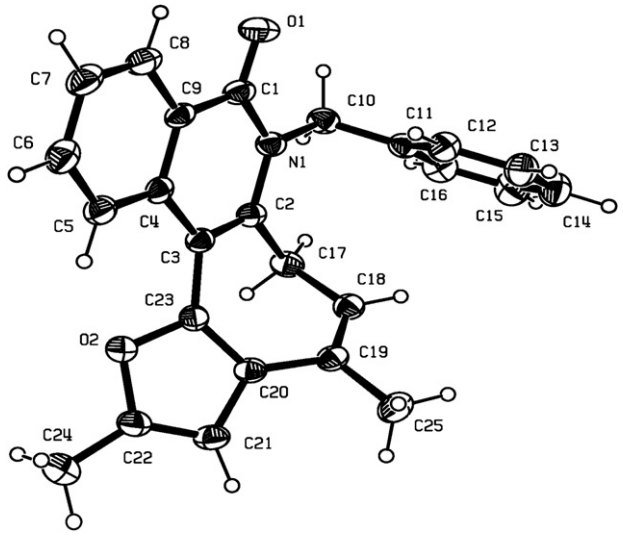


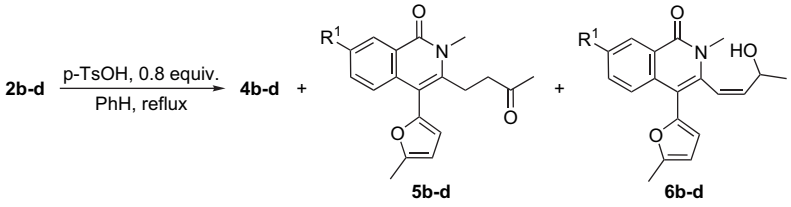
Figure 2. ORTEP diagram of **4h**.

hindrance at the nitrogen atom of the amide group caused by bulky *tert*-butyl substituent. In this case the reaction was accompanied with the strong resinification. In other cases along with the major product **4** we observed by TLC method initially formed intermediates that are present in the reaction mixture in minor amounts and expended during the reaction.

It is known that the reducing of acid concentration in the recyclization of 2-carboxyaryldifurylmethanes **1** into the tetracyclic isochromone derivatives allows raising the selectivity of intermediate ketones' formation.[11c] This prerequisite was used in the synthesis of the corresponding ketones of the isoquinolone series. To our surprise by refluxing amides **2b–d** in 3% benzene solution of *p*-TsOH, the α,β-unsaturated alcohols **6b–d** were isolated from the reaction mixture along with the expected products **4b–d** and **5b–d** (Scheme 4). It should be noted that the formation of allylic alcohols during the recyclizations of *ortho*-substituted benzylfurans was observed for the first time.

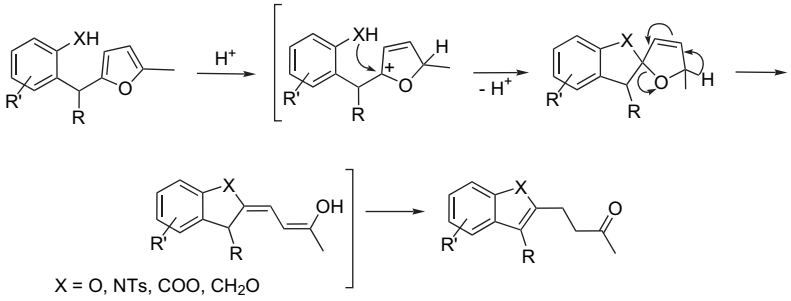
To our knowledge, the α,β-unsaturated alcohols' formation resulting from intramolecular acid-catalyzed recyclization of furan derivatives was already described in literature, although this type of recyclization products is not common.[20] These results and our own experimental data prompted us to specify the possible mechanism of our reaction, which earlier seemed to be similar to the mechanism cited for the recyclization of furans into thiophenes and selenophenes[21] (Scheme 5).

According to this scheme, due to preferential furan ring protonation at the α-position with subsequent *ortho*-nucleophilic



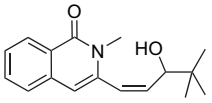
Entry	R^1	Yield (%) 4	5	6
b	Cl	17	29	27
c	Br	14	32	26
d	H	15	31	25

Scheme 4.



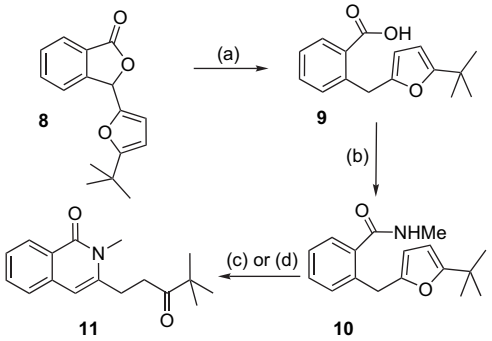
Scheme 5.

attack on electrophilic carbon eventually leading to recyclization product, one can expect the formation of allylic alcohols as the main products. Surprisingly, it is not the case as in most of the reactions of this type corresponding saturated ketones are major products. However, acid-catalyzed isomerizations of allylic alcohols into the corresponding saturated ketones were known for a long time.[22] Assuming that alcohols **6** can be intermediate compounds of the transformation of amides **2** into ketones **5** and in order to study the facility of this process, the compounds **6b–d** were treated with boiling 3% benzene solution of *p*-TsOH. However, only tetracyclic compounds **4b–d** were isolated from the reaction mixture. To avoid intramolecular cyclization and to confirm our assumption, we tried to synthesize alcohol **7** as a model compound.



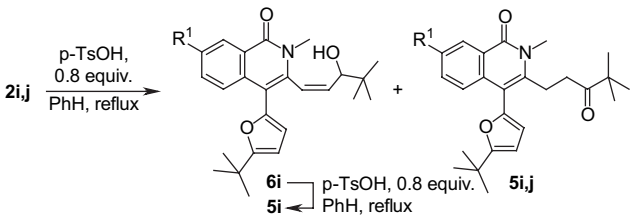
7

We started with 2-furylphthalide **8**[23,11c] that was reduced into the corresponding 2-carboxybenzylfuran **9**[24], which, in turn, was transformed into amide **10** by interaction with $MeNH_2$ in the presence of DCC. The treatment of **10** with boiling 16% benzene solution of *p*-TsOH, as it was expected, smoothly led to ketone **11** in 68% yield (Scheme 6). The lowering of the concentration of *p*-TsOH to 3% rendered the conversion of amide **10** sluggish, but nevertheless the alcohol **7** was not isolated. In the reaction mixture one intermediate was observed by TLC method in negligible amount that rapidly expended during the reaction. Low concentration and the close proximity of R_f of this compound and isoquinolone **11** did not allow us to isolate it for the structural determination.



Scheme 6. (a) Zn, NH_4OH, reflux; (b) DCC, $MeNH_2$, CH_2Cl_2, rt; (c) *p*-TsOH (2.8 equiv), PhH, reflux; (d) *p*-TsOH (0.8 equiv), PhH, reflux.

From our previous work,[11c] it is known that recyclization of 2-carboxyaryldifurylmethanes with *tert*-butyl groups at position 5 of furan rings stops at the corresponding isochromone ketone formation. The second intramolecular cyclization with the participation of 3-oxoalkyl fragments of these ketones is not possible due to the bulky *tert*-butyl substituent at carbonyl group.[11b,c] With this in mind, we have studied the recyclization of amides **2i,j**. Refluxing these amides in 16% benzene solution of *p*-TsOH led to the ketones **5i,j** in 50–52% yields (Scheme 7). Like in the case of amide **10** with reduced *p*-TsOH concentration during recyclization of the amides **2i,j** similar intermediate was observed in the reaction mixture (TLC monitoring), which again had slight difference in R_f with the major product. However, in this case we were lucky and the alcohol **6i** was isolated in minor amount by column chromatography. The treatment of compound **6i** with boiling solution of *p*-TsOH in benzene smoothly led to ketone **5i**.



Entry	R^1	Conditions	Yield (%) 5	6
i	H	2.8 equiv. *p*-TsOH	50	0
j	Br	2.8 equiv. *p*-TsOH	52	0
i	H	0.8 equiv. *p*-TsOH	32	19

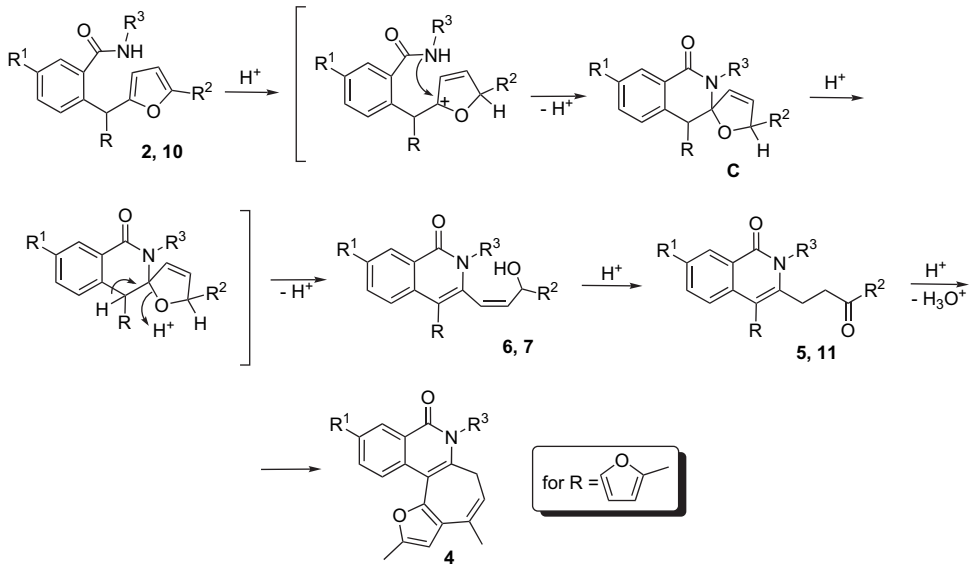
Scheme 7.

Thus, we determined that the recyclization of the amides of 2-carboxybenzylfurans **2** into isoquinolone ketones **5** proceeds via formation of intermediate α,β-unsaturated alcohols **6** and the mechanism of the reaction could be specified (Scheme 8). The reaction starts with the protonation at position 5 of the furan cycle of benzylfuran with subsequent nucleophilic attack of *ortho*-substituent onto furanium cation leading to spiro-structure **C**. The subsequent attack of a proton at the oxygen atom of dihydrofuran ring leads to α,β-unsaturated alcohol formation, which eventually isomerizes into the corresponding ketones **5** and **11** (Scheme 8, compare with Scheme 5). In turn the formation of tetracyclic isoquinolones **4** from ketones **5** proceeds via intramolecular electrophilic cyclization of 3-oxoalkyl substituent at β-position of the furan ring. One cannot exclude from the consideration the cyclization of allyl alcohol into the tetracyclic derivatives. However, the fact that only one isomer, namely tetracyclic isoquinolone **4** with positioning of double bond in the seven-membered ring corresponding to the cyclization of ketone, is an indirect evidence that isomerization of allylic alcohol into saturated ketone precede the cyclization step.

It is obvious that in the case of benzylfurans bearing the other *ortho*-nucleophiles the recyclization reaction also proceeds via the formation of unsaturated alcohols, which were not observed previously because of their rapid isomerization and consequently the low concentration in the reaction mixture or because of R_f coincidence of the mentioned alcohols with the corresponding ketones.

2.3. Synthesis of tetracyclic isoquinolones from isochromones

As a result of recyclization of 2-carboxyaryldifurylmethane amides **2**, we synthesized a new tetracyclic condensed system **4** incorporating isoquinolone nucleus. To the best of our knowledge, a limited number of synthetic works are devoted to the synthesis of isoquinolones conjugated with

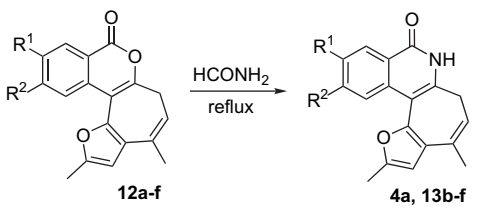


Scheme 8.

seven-membered carbocycle.[25] Obviously, the tetracyclic system **4** is attractive for the medicinal chemists since it includes two pharmacophoric fragments—isoquinolone nucleus and seven-membered carbocycle. Therefore, in our work special attention was paid to the synthesis of tetracyclic isoquinolones unsubstituted at the nitrogen atom meaning the possibility of their further modification.

One of the convenient methods of synthesis of isoquinolone derivatives is transformation of isochromones under the action of amines. In particular, the isoquinolones unsubstituted at the nitrogen atom can be obtained upon treatment of isochromone derivatives with ammonia.[26] The tetracyclic isochromone derivatives **12**, which were obtained by previously developed method in 65–75% yields,[11c] had been used as the starting compounds for the synthesis of isoquinolones **13**. However, known protocols[26] for the replacement of oxygen for nitrogen in our case appeared inefficient.

We have found that the heating of isochromones **12** in formamide for 25–60 min afforded the corresponding isoquinolones **4a** and **13** in good yields (Scheme 9, Table 3). The use of the formamide in the reactions of the transformation of isochromone cycle is not precedented in the literature. The transformation of phthalic anhydride into phthalimide by refluxing in formamide can serve as the close analog of this reaction.[27] It should be mentioned that such route to the tetracyclic isoquinolones **4a** and **13** is more preferable than the recyclization of the corresponding amides since the recyclization of amide **2a** gave product **4a** in only 54% yield.



Scheme 9.

Table 3. Synthesis of isoquinolones **4a**, **13b–f** from isochromones **12a–f**

Entry	R^1	R^2	Compound	Product	Yield (%)
a	H	H	**12a**	**4a**	85
b	Cl	H	**12b**	**13b**	83
c	Br	H	**12c**	**13c**	86
d	I	H	**12d**	**13d**	87
e	OMe	H	**12e**	**13e**	81
f	OMe	OMe	**12f**	**13f**	81

3. Conclusion

We have developed a new approach to the synthesis of isoquinolone derivatives based on the recyclization of amides of the 2-carboxybenzylfurans in the presence of acid catalyst. The scope and limitations of the reaction have been demonstrated. It has been shown that steric hindrance at the nitrogen atom caused by bulky substituents prevents recyclization reaction. We were able to isolate intermediate product of this transformation—the corresponding allylic alcohols. Facile isomerization of such allylic alcohols into the corresponding saturated ketones allowed us to add missing step and specify the mechanism of the recyclization. It is obvious now that the recyclization of other *ortho*-substituted benzylfurans into benzannelated heterocycles, reported previously,[9–12] also proceeds via α,β-unsaturated alcohols formation.

It has been shown that the recyclization of amides of 2-carboxyaryldifurylmethanes can be accompanied with the second intramolecular cyclization, which leads to the new tetracyclic system—furo[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one. The presence of *tert*-butyl group at position 5 of furan cycles precludes this cyclization for steric reasons. The tetracyclic isoquinolone derivatives were obtained also by the alternative synthesis starting with the corresponding isochromones by refluxing them in formamide. Such method of transformation of isochromones into isoquinolones was not described in literature.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 on a Bruker AC 200, Bruker WM 250, and Bruker AM 300 spectrometers. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard and coupling constants (J) are given as absolute values in hertz to the nearest 0.1 Hz. Mass spectra were recorded on a Kratos MS-30 instrument with 70 eV electron impact ionization at 200 °C. IR spectra were measured as KBr plates on InfraLUM FT-02 and InfraLUM FT-801 instruments. Column chromatography was carried out using silica gel KSK (5–40 μm) manufactured by LTD Sorbpolymer.

4.2. General procedure for the synthesis of amides 2a–j

The mixture of acid **1** (0.01 mol), DCC (2.27 g, 0.011 mol), and CH_2Cl_2 (90 cm^3) was stirred for 10 min at room temperature. Then amine (0.015 mol) or its concentrated aqueous solution was added. Then stirring was continued for 20–30 min and after it the mixture was filtered off from the dicyclohexylurea. The filtrate was evaporated. The amide **2a–i** was isolated from the mixture by column chromatography (silica gel, eluent: hexane–AcOEt, 4:1).

4.2.1. 2-Bis(5-methyl-2-furyl)methylbenzamide (2a). Yield 0.97 g, 33% as a colorless crystals, mp 148–149 °C (from hexane–AcOEt). [Found: C, 73.12; H, 5.75. $C_{18}H_{17}NO_3$ requires: C, 73.20; H, 5.80%.] ν_{max} (KBr) 3332, 3171, 1650, 1619, 779, 744 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.51–7.54 (1H, m, H_{Ar}), 7.30–7.45 (3H, m, H_{Ar}), 6.04 (1H, s, C*H*), 5.89 (2H, d, *J* 3.1 Hz, 3-H_{fur}), 5.88 (2H, d, *J* 3.1 Hz, 4-H_{fur}), 5.80 (2H, br s, NH_2), 2.24 (6H, s, *Me*).

4.2.2. 5-Chloro-*N*-methyl-2-bis(5-methyl-2-furyl)methylbenzamide (2b). Yield 1.20 g, 35% as a colorless crystals, mp 147–148 °C (from hexane–AcOEt). [Found: C, 66.44; H, 5.21. $C_{19}H_{18}ClNO_3$ requires: C, 66.38; H, 5.28%.] ν_{max} (KBr) 3299, 1638, 1555, 1319, 782, 768 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.32 (1H, dd, *J* 2.0, 8.5 Hz, H_{Ar}), 7.24 (1H, d, *J* 8.5 Hz, H_{Ar}), 5.91 (2H, d, *J* 3.1 Hz, 3-H_{fur}), 5.88 (2H, d, *J* 3.1 Hz, 4-H_{fur}), 5.81 (1H, br s, N*H*), 5.83 (1H, s, C*H*), 2.92 (3H, d, *J* 4.9 Hz, NH*Me*), 2.23 (6H, s, *Me*).

4.2.3. 5-Bromo-*N*-methyl-2-bis(5-methyl-2-furyl)methylbenzamide (2c). Yield 1.24 g, 32% as a colorless crystals, mp 150–151 °C (from hexane–AcOEt). [Found: C, 58.85; H, 4.60. $C_{19}H_{18}BrNO_3$ requires: C, 58.78; H, 4.67%.] ν_{max} (KBr) 3296, 1636, 1587, 1552, 1408, 1317, 1217, 1022, 867, 782, 706, 688 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.55 (1H, d, *J* 2.0 Hz, H_{Ar}), 7.47 (1H, dd, *J* 2.0, 8.3 Hz, H_{Ar}), 7.18 (1H, d, *J* 8.3 Hz, H_{Ar}), 5.91 (2H, d, *J* 3.1 Hz, 3-H_{fur}), 5.88 (2H, d, *J* 3.1 Hz, 4-H_{fur}), 5.82 (1H, s, C*H*), 5.77 (1H, br s, N*H*), 2.92 (3H, d, *J* 4.9 Hz, NH*Me*), 2.23 (6H, s, *Me*).

4.2.4. *N*-Methyl-2-bis(5-methyl-2-furyl)methylbenzamide (2d). Yield 0.93 g, 30% as a colorless crystals, mp 120–121 °C (from hexane–AcOEt). [Found: C, 73.88; H, 6.10. $C_{19}H_{19}NO_3$ requires: C, 73.77; H, 6.19%.] ν_{max} (KBr) 3278, 1646, 1543, 1406, 1316, 1216, 1022, 948, 779, 717 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.23–7.43 (4H, m, H_{Ar}), 5.91 (2H, d, *J* 3.1 Hz, 3-H_{fur}), 5.89 (2H, d, *J* 3.1 Hz, 4-H_{fur}), 5.88 (1H, s, C*H*), 5.80 (1H, br s, N*H*), 2.92 (3H, d, *J* 4.9 Hz, NH*Me*), 2.25 (6H, s, *Me*).

4.2.5. *N*-Ethyl-2-bis(5-methyl-2-furyl)methylbenzamide (2e). Yield 1.16 g, 36% as a colorless crystals, mp 131–132 °C (from hexane–AcOEt). [Found: C, 74.20; H, 6.63. $C_{20}H_{21}NO_3$ requires: C, 74.28; H, 6.55%.] ν_{max} (KBr) 3264, 1632, 1559, 1439, 1320, 1214, 1024, 783, 730 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.25–7.44 (4H, m, H_{Ar}), 5.93 (1H, s, C*H*), 5.88 (4H, s, H_{fur}), 5.75 (1H, br s, N*H*), 3.42 (2H, dq, *J* 4.9, 7.2 Hz, CH_2Me), 2.24 (6H, s, *Me*), 1.14 (3H, t, *J* 7.2 Hz, CH$_2$*Me*).

4.2.6. *N*-Isopropyl-2-bis(5-methyl-2-furyl)methylbenzamide (2f). Yield 1.15 g, 34% as a colorless crystals, mp 116–117 °C (from hexane–AcOEt). [Found: C, 74.64; H, 6.88. $C_{21}H_{23}NO_3$ requires: C, 74.75; H, 6.87%.] ν_{max} (KBr) 3244, 1624, 1558, 1216, 1021, 778, 731 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.43–7.46 (1H, m, H_{Ar}), 7.29–7.35 (3H, m, H_{Ar}), 5.88 (4H, s, H_{fur}), 5.86 (1H, s, C*H*), 5.61 (1H, br s, N*H*), 4.19–4.26 (1H, m, C*H*(Me)$_2$), 2.24 (6H, s, *Me*), 1.16 (6H, d, *J* 7.2 Hz, CH(*Me*)$_2$).

4.2.7. *N*-(*tert*-Butyl)-2-bis(5-methyl-2-furyl)methylbenzamide (2g). Yield 1.12 g, 32% as a colorless crystals, mp 102–103 °C (from hexane–AcOEt). [Found: C, 75.29; H, 7.24. $C_{22}H_{25}NO_3$ requires: C, 75.19; H, 7.17%.] ν_{max} (KBr) 3335, 1641, 1525, 1450, 1365, 1310, 1221, 1021, 780, 745 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41–7.44 (1H, m, H_{Ar}), 7.24–7.33 (3H, m, H_{Ar}), 5.85–5.87 (5H, m, H_{fur}+C*H*), 5.52 (1H, br s, N*H*), 2.25 (6H, s, *Me*), 1.38 (9H, s, *t-Bu*).

4.2.8. *N*-Benzyl-2-bis(5-methyl-2-furyl)methylbenzamide (2h). Yield 1.35 g, 35% as a colorless crystals, mp 88–89 °C (from hexane–AcOEt). [Found: C, 77.81; H, 6.09. $C_{25}H_{23}NO_3$ requires: C, 77.90; H, 6.01%.] ν_{max} (KBr) 3213, 1629, 1600, 1558, 1318, 1216, 1022, 780, 733, 699; δ_H (300 MHz, $CDCl_3$) 7.46–7.48 (1H, m, H_{Ar}), 7.26–7.38 (8H, m, H_{Ar}), 6.10 (1H, br s, N*H*), 5.97 (1H, s, C*H*), 5.86 (4H, s, H_{fur}), 4.58 (2H, d, *J* 5.4 Hz, CH_2), 2.20 (6H, s, *Me*).

4.2.9. *N*-Methyl-2-bis(5-(*tert*-butyl)-2-furyl)methylbenzamide (2i). Yield 1.30 g, 33% as a colorless crystals, mp 141–142 °C (from hexane–AcOEt). [Found: C, 76.43; H, 7.85. $C_{25}H_{31}NO_3$ requires: C, 76.30; H, 7.94%.]; ν_{max} (KBr) 3346, 1648, 1554, 1477, 1300, 1191, 1126, 1010, 772, 728, 681 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.42–7.44 (1H, m, H_{Ar}), 7.26–7.33 (4H, m, H_{Ar}), 5.86 (5H, s, H_{fur}+C*H*), 5.65 (1H, br s, N*H*), 2.92 (3H, d, *J* 4.9 Hz, *Me*), 1.23 (18H, s, *t-Bu*).

4.2.10. 5-Bromo-*N*-methyl-2-bis(5-(*tert*-butyl)-2-furyl)-methylbenzamide (2j). Yield 1.60 g, 34% as a yellow oil. [Found: C, 63.69; H, 6.30. $C_{25}H_{30}BrNO_3$ requires: C, 63.56; H, 6.40%.] ν_{max} (KBr) 3296, 1639, 1558, 1318, 1195, 1013, 777; δ_H (300 MHz, $CDCl_3$) 7.58 (1H, d, *J* 2.1 Hz, H_{Ar}), 7.45 (1H, dd, *J* 2.1, 8.3 Hz, H_{Ar}), 7.15 (1H, d, *J* 8.3 Hz, H_{Ar}), 5.86 (4H, s, H_{fur}), 5.80 (1H, br s, N*H*), 5.79 (1H, s, C*H*), 2.92 (3H, d, *J* 4.9 Hz, *Me*), 1.23 (18H, s, *t-Bu*).

4.3. General procedure for the synthesis of compounds 4a–h

Amide **2** (0.01 mol) was refluxed within 25 min in 16% solution of anhydrous *p*-TsOH in benzene (30 cm^3), prepared by azeotropic removal of water from a solution of *p*-TsOH in benzene. The reaction mixture was poured into excess of water and extracted with CH_2Cl_2. Extract was evaporated to dryness and the residue separated by column chromatography (silica gel, eluent: hexane–AcOEt, 4:1).

4.3.1. 2,4-Dimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (4a). Yield 1.50 g, 54% as a yellowish crystals, mp >310 °C (decomp.) [from EtOH–1,4-dioxane]. [Found: C, 77.90; H, 5.36. $C_{18}H_{15}NO_2$ requires: C, 77.96; H, 5.45%.] ν_{max} (KBr) 1656, 1612, 1472, 911, 829, 773 cm^{-1}; δ_H (300 MHz, DMSO) 11.61 (1H, s, N*H*), 8.36–8.38 (1H, m, H_{Ar}), 8.25–8.27 (1H, m, H_{Ar}), 7.72–7.77 (1H, m, H_{Ar}), 7.47–7.52 (1H, m, H_{Ar}), 6.45 (1H, s, H_{fur}), 5.36 (1H, t, *J* 6.7 Hz, =C*H*), 2.92 (2H, d, *J* 6.7 Hz, CH_2), 2.46 (3H, s, *Me*), 1.98 (3H, s, *Me*); δ_C (75 MHz, DMSO, 65 °C) 161.4, 149.5, 147.5, 134.7, 134.6, 132.1, 130.8, 126.7, 125.1, 124.8, 124.1, 123.7, 115.5, 105.1, 103.1, 30.1, 19.3, 12.8; MS: *m/z* (%) 278 (M^++1, 19), 277 (M^+, 100), 276 (32), 263 (17), 262 (87), 232 (6), 204 (6).

4.3.2. 10-Chloro-2,4,7-trimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (4b). Yield 1.85 g, 57% as a yellowish crystals, mp 216–217 °C (from hexane–AcOEt). [Found: C, 70.10; H, 4.83. $C_{19}H_{16}ClNO_2$ requires: C, 70.05; H, 4.95%.] ν_{max} (KBr) 1655, 1605, 1473, 899, 819 cm^{-1}; δ_H (300 MHz, DMSO) 8.39 (1H, d, *J* 9.0 Hz, H_{Ar}), 8.22 (1H, d, *J* 2.3 Hz, H_{Ar}), 7.75 (1H, dd, *J* 2.3, 9.0 Hz, H_{Ar}), 6.51 (1H, s, H_{fur}), 5.55 (1H, t, *J* 6.8 Hz, =C*H*), 3.73 (3H, s, *Me*), 2.49 (2H, d, *J* 6.8 Hz, CH_2), 2.48 (3H, s, *Me*), 2.01 (3H, s, *Me*); δ_C (50 MHz, DMSO, 60 °C) 160.4, 150.3, 147.4, 135.4, 132.3, 131.2, 130.4, 128.3, 126.3, 126.1, 124.5, 119.3, 114.7, 105.3, 104.1, 32.2, 29.4, 19.2, 13.1; MS: *m/z* (%) 328/326 (M^++1, 7/24), 327/325 (M^+, 35/100), 313 (12), 312/310 (24/71), 282 (15), 280 (19).

4.3.3. 10-Bromo-2,4,7-trimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (4c). Yield 2.11 g, 57% as a yellowish crystals, mp 255–256 °C (from hexane–AcOEt). [Found: C, 61.58; H, 4.40. $C_{19}H_{16}BrNO_2$ requires: C, 61.64; H, 4.36%.] ν_{max} (KBr) 1643, 1577, 1478, 1412, 915, 824, 798 cm^{-1}; δ_H (300 MHz, DMSO) 8.38 (1H, d, *J* 2.2 Hz, H_{Ar}), 8.33 (1H, d, *J* 8.9 Hz, H_{Ar}), 7.87 (1H, dd, *J* 2.2, 8.9 Hz, H_{Ar}), 6.51 (1H, s, H_{fur}), 5.55 (1H, t, *J* 6.9 Hz, =C*H*), 3.73 (3H, s, *Me*), 2.49 (2H, d, *J* 6.9 Hz, CH_2), 2.48 (3H, s, *Me*), 2.01 (3H, s, *Me*); δ_C (50 MHz, DMSO, 50 °C) 160.3, 150.4, 147.5, 135.7, 135.1, 132.3, 131.3, 129.6, 126.3 (2C), 124.9, 118.7, 114.8, 105.4, 104.2, 32.3, 29.5, 19.3, 13.2; MS: *m/z* (%) 372/370 (M^++1, 24/28), 371/369 (M^+, 96/100), 368 (18), 357 (17), 356 (86), 355 (12), 354 (94), 328 (21), 326 (20), 252(16), 247 (20), 246 (14), 219 (19).

4.3.4. 2,4,7-Trimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (4d). Yield 1.60 g, 55% as a yellowish crystals, mp 183–184 °C (from hexane–AcOEt). [Found: C, 78.28; H, 5.95. $C_{19}H_{17}NO_2$ requires: C, 78.33; H, 5.88%.] ν_{max} (KBr) 1650, 1581, 1550, 1484, 1413, 1334, 832, 773, 691 cm^{-1}; δ_H (300 MHz, DMSO) 8.37–8.40 (1H, m, H_{Ar}), 8.29–8.32 (1H, m, H_{Ar}), 7.71–7.76 (1H, m, H_{Ar}), 7.47–7.52 (1H, m, H_{Ar}), 6.51 (1H, s, H_{fur}), 5.55 (1H, t, *J* 7.0 Hz, =C*H*), 3.74 (3H, s, *Me*), 2.49 (2H, d, *J* 7.0 Hz, CH_2), 2.48 (3H, s, *Me*), 2.01 (3H, s, *Me*); δ_C (50 MHz, DMSO) 161.5, 150.1, 148.1, 135.1, 133.4, 132.4, 131.2, 127.6, 126.1, 125.8, 123.8, 123.3, 114.9, 105.4, 104.6, 32.1, 29.5, 19.4, 13.3; MS: *m/z* (%) 292 (M^++1, 27), 291 (M^+, 100), 290 (46), 277 (22), 276 (99), 248 (24), 247 (18), 246 (23), 232 (15), 219 (13), 204 (14).

4.3.5. 7-Ethyl-2,4-dimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (4e). Yield 1.68 g, 55% as a yellowish crystals, mp 146–147 °C (from hexane–AcOEt). [Found: C, 78.67; H, 6.20. $C_{20}H_{19}NO_2$ requires: C, 78.66; H, 6.27%.] ν_{max} (KBr) 1645, 1606, 1550, 1483, 1446, 1340, 1171, 852, 777 cm^{-1}; δ_H (300 MHz, DMSO) 8.34–8.37 (1H, m, H_{Ar}), 8.29–8.31 (1H, m, H_{Ar}), 7.70–7.75 (1H, m, H_{Ar}), 7.47–7.52 (1H, m, H_{Ar}), 6.50 (1H, s, H_{fur}), 5.51–5.56 (1H, m, =C*H*), 4.20–4.48 (2H, br m, CH_2Me), 3.55–3.75 (1H, br m, CH_2), 2.48 (3H, s, *Me*), 2.20–2.40 (1H, br m, CH_2), 2.00 (3H, s, *Me*), 1.30–1.35 (3H, m, CH_2*Me*); δ_C (50 MHz, DMSO) 161.1, 150.3, 148.2, 135.3, 133.6, 132.7, 131.3, 127.7, 126.1 (2C), 124.0, 123.4, 116.2, 105.5, 104.9, 39.8, 29.3, 19.5, 14.0, 13.5; MS: *m/z* (%) 306 (M^++1, 25), 305 (M^+, 100), 304 (29), 291 (21), 290 (91), 277 (32), 276 (59), 262 (59), 260 (14), 247 (19), 246 (24), 232 (26).

4.3.6. 7-Isopropyl-2,4-dimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (4f). Yield 1.44 g, 45% as a yellowish crystals, mp 166–167 °C (from hexane–AcOEt). [Found: C, 78.91; H, 6.68. $C_{21}H_{21}NO_2$ requires: C, 78.97; H, 6.63%.] ν_{max} (KBr) 1640, 1603, 1546, 1451, 1361, 1325, 1176, 1083, 1037, 956, 853, 774, 694 cm^{-1}; δ_H (300 MHz, DMSO) 8.27–8.29 (2H, m, H_{Ar}), 7.68–7.73 (1H, m, H_{Ar}), 7.45–7.50 (1H, m, H_{Ar}), 6.50 (1H, s, H_{fur}), 5.53–5.58 (1H, m, =C*H*), 5.07–5.22 (1H, br m, C*H*(Me)$_2$), 3.62–3.78 (1H, br m, CH_2), 2.47 (3H, s, *Me*), 2.16–2.32 (1H, br m, CH_2), 2.03 (3H, s, *Me*), 1.52–1.71 (6H, br m, CH(*Me*)$_2$); δ_C (75 MHz, DMSO) 161.6, 150.2, 148.3, 135.2, 133.3, 132.4, 131.2, 127.4, 126.4, 126.0, 124.4, 123.8, 116.4, 105.5 (2C), 50.5, 29.8, 20.1, 19.5, 13.5 (2C); MS: *m/z* (%) 320 (M^++1, 9), 319 (M^+, 58), 278 (36), 277 (100), 276 (63), 262 (20), 261 (100), 246 (17), 234 (15).

4.3.7. 7-Benzyl-2,4-dimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (4h). Yield 2.02 g, 55% as a yellowish crystals, mp 197–198 °C (from hexane–AcOEt). [Found: C, 81.53; H, 5.89. $C_{25}H_{21}NO_2$ requires: C, 81.72; H, 5.76%.] ν_{max} (KBr) 1651, 1602, 1481, 1394, 1163, 778, 740, 706 cm^{-1}; δ_H (300 MHz, DMSO) 8.36–8.42 (2H, m, H_{Ar}), 7.76–7.81 (1H, m, H_{Ar}), 7.53–7.58 (1H, m, H_{Ar}), 7.21–7.39 (5H, m, *Ph*), 6.47 (1H, s, H_{fur}), 5.61 (2H, br s, CH_2Ph), 4.90–5.01 (1H, m, =C*H*), 3.41–3.60 (1H, br m, CH_2), 2.47 (3H, s, *Me*), 2.12–2.31 (1H, br m, CH_2), 1.90 (3H, s, *Me*); δ_C (75 MHz, DMSO) 161.9, 150.4, 147.9, 137.1, 135.3, 133.8, 133.1, 130.9, 128.7 (2C), 128.0, 127.1, 126.4 (4C), 124.1, 123.4, 115.7, 105.6, 105.2, 47.3, 29.9, 19.5, 13.5; MS: *m/z* (%) 368 (M^++1, 16), 367 (M^+, 76), 277 (20), 276 (100), 91 (22).

4.4. General procedure for the synthesis of compounds 5b–d,i and 6b–d,i

Amide **3** (0.01 mol) was refluxed within 25 min in 3% solution of anhydrous *p*-TsOH in benzene (60 cm^3), prepared by azeotropic removal of water from a solution of *p*-TsOH in benzene. The reaction mixture was poured into excess of water and extracted with CH_2Cl_2. Extract was evaporated to dryness and the residue separated by column chromatography (silica gel, eluent: hexane–AcOEt, 4:1) giving compounds **4**–**6**.

4.4.1. 7-Chloro-2-methyl-4-(5-methyl-2-furyl)-3-(3-oxobutyl)isoquinolin-1(2*H*)-one (5b). Yield 1.00 g, 29% as a yellowish crystals, mp 120–122 °C (from hexane–AcOEt). [Found: C, 66.32; H, 5.35. $C_{19}H_{18}ClNO_3$ requires: C, 66.38; H, 5.28%.] ν_{max} (KBr) 1708, 1658, 1480, 1169, 1038, 1018, 910, 826, 787 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.39 (1H, d, *J* 2.1 Hz, H_{Ar}), 7.48 (1H, dd, *J* 2.1, 8.7 Hz, H_{Ar}), 7.21 (1H, d, *J* 8.7 Hz, H_{Ar}), 6.27 (1H, d, *J* 3.0 Hz, 3-H_{fur}), 6.12 (1H, d, *J* 3.0 Hz, 4-H_{fur}), 3.65 (3H, s, *Me*), 2.88–2.94 (2H, m, C*H*$_2$), 2.70–2.75 (2H, m, C*H*$_2$), 2.34 (3H, s, *Me*), 2.16 (3H, s, *Me*); δ_C (50 MHz, $CDCl_3$) 208.8, 162.0, 152.5, 146.5, 144.2, 135.5, 132.7, 132.4, 127.1, 126.3, 125.0, 112.3, 108.2, 107.0, 42.7, 31.7, 30.0, 25.5, 13.7; MS: *m*/*z* (%) 346/344 (M^++1, 7/23), 345/343 (M^+, 38/100), 302 (22), 300 (57), 288 (14), 286 (39), 285 (14), 258 (35), 256 (14), 244 (17), 243 (18), 223 (14).

4.4.2. 7-Bromo-2-methyl-4-(5-methyl-2-furyl)-3-(3-oxobutyl)isoquinolin-1(2*H*)-one (5c). Yield 1.24 g, 32% as a yellowish crystals, mp 125–127 °C (from hexane–AcOEt). [Found: C, 58.72; H, 4.61. $C_{19}H_{18}BrNO_3$ requires: C, 58.78; H, 4.67%.] ν_{max} (KBr) 1712, 1651, 1590, 1474, 1367, 1315, 1215, 1022, 961, 829 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.55 (1H, d, *J* 2.1 Hz, H_{Ar}), 7.62 (1H, dd, *J* 2.1, 8.7 Hz, H_{Ar}), 7.14 (1H, d, *J* 8.7 Hz, H_{Ar}), 6.27 (1H, d, *J* 3.0 Hz, 3-H_{fur}), 6.12 (1H, d, *J* 3.0 Hz, 4-H_{fur}), 3.65 (3H, s, *Me*), 2.87–2.93 (2H, m, C*H*$_2$), 2.71–2.76 (2H, m, C*H*$_2$), 2.34 (3H, s, *Me*), 2.17 (3H, s, *Me*); δ_C (50 MHz, $CDCl_3$) 205.8, 161.9, 152.5, 146.4, 144.5, 135.9, 135.5, 130.3, 126.4, 125.3, 120.3, 112.4, 108.3, 107.0, 42.7, 31.7, 29.9, 25.5, 13.8; MS: *m*/*z* (%) 390/388 (M^++1, 9/10), 389/387 (M^+, 41/41), 346/344 (22/22), 143 (23), 99 (43), 98 (25).

4.4.3. 2-Methyl-4-(5-methyl-2-furyl)-3-(3-oxobutyl)isoquinolin-1(2*H*)-one (5d). Yield 0.96 g, 31% as a yellowish crystals, mp 136–137 °C (from hexane–AcOEt). [Found: C, 73.70; H, 6.13. $C_{19}H_{19}NO_3$ requires: C, 73.77; H, 6.19%.] ν_{max} (KBr) 1710, 1651, 1591, 1547, 1481, 1419, 1370, 1324, 1168, 1024, 801, 767, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.41–8.43 (1H, m, H_{Ar}), 7.53–7.55 (1H, m, H_{Ar}), 7.41–7.46 (1H, m, H_{Ar}), 7.25–7.27 (1H, m, H_{Ar}), 6.28 (1H, d, *J* 3.0 Hz, 3-H_{fur}), 6.12 (1H, d, *J* 3.0 Hz, 4-H_{fur}), 3.66 (3H, s, *Me*), 2.89–2.94 (2H, m, C*H*$_2$), 2.71–2.76 (2H, m, C*H*$_2$), 2.35 (3H, s, *Me*), 2.16 (3H, s, *Me*); δ_C (50 MHz, $CDCl_3$) 206.0, 163.2, 152.3, 147.0, 143.8, 137.2, 132.4, 127.8, 126.5, 124.4, 124.0, 112.1, 108.7, 106.9, 42.9, 31.5, 29.9, 25.5, 13.8; MS: *m*/*z* (%) 310 (M^++1, 24), 309 (M^+, 100), 265 (77), 252 (40), 248 (22), 233 (16), 224 (52), 223 (25), 222 (18), 210 (15), 209 (31), 99 (15).

4.4.4. 7-Chloro-3-((*Z*)-3-hydroxy-1-butenyl)-2-methyl-4-(5-methyl-2-furyl)isoquinolin-1(2*H*)-one (6b). Yield 0.93 g, 27% as a yellowish crystals, mp 144–145 °C (from hexane–AcOEt). [Found: C, 66.31; H, 5.22. $C_{19}H_{18}ClNO_3$ requires: C, 66.38; H, 5.28%.] ν_{max} (KBr) 3395, 2924, 1627, 1588, 1481, 1343, 1054, 968, 906, 823, 794, 594 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.40 (1H, d, *J* 1.7 Hz, H_{Ar}), 7.51 (1H, dd, *J* 1.7, 8.7 Hz, H_{Ar}), 7.36 (1H, d, *J* 8.7 Hz, H_{Ar}), 6.24 (1H, d, *J* 3.0 Hz, 3-H_{fur}), 6.18 (1H, d, *J* 11.3 Hz, =C*H*), 6.12 (1H, d, *J* 3.0 Hz, 4-H_{fur}), 5.76 (1H, dd, *J* 9.0, 11.3 Hz, =C*H*), 4.26–4.31 (1H, m, C*H*), 3.57 (3H, s, *Me*), 2.36 (3H, s, *Me*), 1.65 (1H, br s, O*H*), 1.12 (3H, d, *J* 6.2 Hz, *Me*); δ_C (50 MHz, $CDCl_3$) 161.6, 152.5, 146.7, 140.1 (2C), 135.0, 132.9, 127.2, 126.5, 125.5, 122.2 (2C), 108.2. 112.3, 107.1, 64.6, 33.1, 21.9, 13.7; MS: *m*/*z* (%) 345/343 (M^+, 10/30), 301 (28), 300 (44), 299 (72), 298 (100), 286 (17), 284 (33), 282 (32), 271 (17), 270 (22), 257 (15), 256 (23), 186 (24).

4.4.5. 7-Bromo-3-((*Z*)-3-hydroxy-1-butenyl)-2-methyl-4-(5-methyl-2-furyl)isoquinolin-1(2*H*)-one (6c). Yield 1.01 g, 26% as a yellowish crystals, mp 144–145 °C (from hexane–AcOEt). [Found: C, 58.72; H, 4.73. $C_{19}H_{18}BrNO_3$ requires: C, 58.78; H, 4.67%.] ν_{max} (KBr) 3417, 2923, 1626, 1584, 1477, 1341, 1223, 1126, 1055, 967, 902, 794, 748, 594; δ_H (300 MHz, $CDCl_3$) 8.59 (1H, d, *J* 1.8 Hz, H_{Ar}), 7.66 (1H, dd, *J* 1.8, 8.7 Hz, H_{Ar}), 7.30 (1H, d, *J* 8.7 Hz, H_{Ar}), 6.24 (1H, d, *J* 3.0 Hz, 3-H_{fur}), 6.17 (1H, d, *J* 11.3 Hz, =C*H*), 6.12 (1H, d, *J* 3.0 Hz, 4-H_{fur}), 5.76 (1H, dd, *J* 9.0, 11.3 Hz, =C*H*), 4.26–4.31 (1H, m, C*H*), 3.58 (3H, s, *Me*), 2.36 (3H, s, *Me*), 1.56 (1H, br s, O*H*), 1.13 (3H, d, *J* 6.2 Hz, *Me*); δ_C (50 MHz, $CDCl_3$) 161.4, 152.5, 146.6, 140.3, 140.1, 135.6, 135.3, 130.4, 126.6, 125.8, 122.2, 120.8, 112.3, 108.0, 107.1, 64.6, 33.2, 21.9, 13.7; MS: *m*/*z* (%) 389/387 (M^+, 6/6), 346 (10), 345 (48), 344 (99), 343 (42), 342 (100), 330 (15), 328 (25), 326 (18), 262 (20), 220 (16).

4.4.6. 3-((*Z*)-3-Hydroxy-1-butenyl)-2-methyl-4-(5-methyl-2-furyl)isoquinolin-1(2*H*)-one (6d). Yield 0.77 g, 25% as a yellowish crystals, mp 170–171 °C (from hexane–AcOEt). [Found: C, 73.84; H, 6.11. $C_{19}H_{19}NO_3$ requires: C, 73.77; H, 6.19%.] ν_{max} (KBr) 3409, 2964, 1631, 1557, 1340, 1217, 1122, 1056, 1023, 801, 694 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.45–8.48 (1H, m, H_{Ar}), 7.58–7.63 (1H, m, H_{Ar}), 7.41–7.51 (2H, m, H_{Ar}), 6.25 (1H, d, *J* 3.0 Hz, 3-H_{fur}), 6.20 (1H, d, *J* 11.3 Hz, =C*H*), 6.12 (1H, d, *J* 3.0 Hz, 4-H_{fur}), 5.75 (1H, dd, *J* 9.0, 11.3 Hz, =C*H*), 4.26–4.33 (1H, m, C*H*), 3.59 (3H, s, *Me*), 2.36 (3H, s, *Me*), 1.60 (1H, s, O*H*), 1.12 (3H, d, *J* 6.2 Hz, *Me*); δ_C (50 MHz, $CDCl_3$) 162.6, 152.2, 147.2, 139.9, 139.8, 136.6, 132.4, 127.8, 126.9, 124.7, 124.4, 122.3, 112.1, 108.1, 107.0, 64.6, 33.0, 21.9, 13.7; MS: *m*/*z* (%) 309 (M^+, 15), 264 (61), 263 (100), 250 (33), 249 (14), 248 (56), 236 (22), 223 (25), 222 (34), 220 (15), 192 (18).

4.4.7. 4-(5-(*tert*-Butyl)-2-furyl)-3-(4,4-dimethyl-3-oxopentyl)-2-methylisoquinolin-1(2*H*)-one (5i). Ketone **5i** was obtained analogous to **4a**–**h** within 10 min. Yield 1.97 g, 50% as a yellowish crystals, mp 115–116 °C (from hexane–AcOEt). [Found: C, 76.38; H, 7.99. $C_{25}H_{31}NO_3$ requires: C, 76.30; H, 7.94%.] ν_{max} (KBr) 1698, 1654, 1586, 1548, 1476, 1365, 1080, 1024, 971, 768, 698 cm^{-1}; δ_H (300 MHz, DMSO) 8.24–8.27 (1H, m, H_{Ar}), 7.61–7.69 (1H, m, H_{Ar}), 7.43–7.51 (1H, m, H_{Ar}), 7.09–7.12 (1H, m, H_{Ar}), 6.41 (1H,

d, *J* 3.1 Hz, 3-H_{fur}), 6.21 (1H, d, *J* 3.1 Hz, 4-H_{fur}), 3.60 (3H, s, *Me*), 2.81–2.84 (4H, m, CH_2CH_2), 1.27 (9H, s, *t-Bu*), 1.07 (9H, s, *t-Bu*); δ_C (50 MHz, DMSO) 213.3, 163.5, 161.7, 146.5, 145.2, 136.7, 132.5, 127.2, 126.3, 123.8, 123.2, 111.4, 106.9, 103.3, 43.4, 35.6, 32.3, 31.0, 28.8 (3C), 26.0 (3C), 25.7; MS: *m/z* (%) 394 (M^++1, 20), 393 (M^+, 100), 378 (33), 308 (13), 222 (11), 57 (22).

4.4.8. 7-Bromo-4-(5-(*tert*-butyl)-2-furyl)-3-(4,4-dimethyl-3-oxopentyl)-2-methylisoquinolin-1(2*H*)-one (5j). Ketone **5j** was obtained analogous to **4a–h** within 10 min. Yield 2.45 g, 52% as a yellowish crystals, mp 185–186 °C (from hexane–AcOEt). [Found: C, 63.50; H, 6.47. $C_{25}H_{30}BrNO_3$ requires: C, 63.56; H, 6.40%.] ν_{max} (KBr) 1700, 1640, 1540, 1477, 1364, 1188, 1080, 986, 820, 784 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.53 (1H, d, *J* 2.1 Hz, H_{Ar}), 7.60 (1H, dd, *J* 2.1, 8.7 Hz, H_{Ar}), 7.06 (1H, d, *J* 8.7 Hz, H_{Ar}), 6.25 (1H, d, *J* 3.0 Hz, 3-H_{fur}), 6.09 (1H, d, *J* 3.0 Hz, 4-H_{fur}), 3.64 (3H, s, *Me*), 2.88–2.93 (2H, m, CH_2), 2.71–2.76 (2H, m, CH_2), 1.29 (9H, s, *t-Bu*), 1.11 (9H, s, *t-Bu*); δ_C (50 MHz, $CDCl_3$) 213.4, 164.7, 162.0, 146.3, 144.7, 136.1, 135.5, 130.2, 126.4, 125.3, 120.2, 111.7, 108.4, 103.2, 44.1, 36.0, 32.7, 31.6, 29.1 (3C), 26.4 (3C), 26.0; MS: *m/z* (%) 474/472 (M^++1, 15/16), 473/471 (M^+, 100/100), 458 (20), 456 (20), 388 (23), 386 (23), 358 (15), 356 (15), 302 (28), 300 (28), 57 (81).

4.4.9. 4-(5-(*tert*-Butyl)-2-furyl)-3-((*Z*)-3-hydroxy-4,4-dimethyl-1-pentenyl)-2-methylisoquinolin-1(2*H*)-one (6i). Alcohol **6i** was prepared analogous to **6b–d** as a white solid with 90% purity and characterized by ^1H NMR only. δ_H (300 MHz, $CDCl_3$) 8.48–8.50 (1H, m, H_{Ar}), 7.60–7.65 (1H, m, H_{Ar}), 7.48–7.55 (2H, m, H_{Ar}), 6.37 (1H, d, *J* 11.5 Hz, =C*H*), 6.29 (1H, d, *J* 3.0 Hz, 3-H_{fur}), 6.12 (1H, d, *J* 3.0 Hz, 4-H_{fur}), 5.79 (1H, dd, *J* 9.1, 11.5 Hz, =C*H*), 3.61–3.66 (1H, m, C*H*), 3.61 (3H, s, *Me*), 1.71 (1H, br s, O*H*), 1.34 (9H, s, *t-Bu*), 0.79 (9H, s, *t-Bu*).

4.5. *N*-Methyl-2-(5-(*tert*-butyl)-2-furyl)methylbenzamide (10)

Amide **10** was obtained analogous to compounds **2a–j**. Yield 0.95 g, 35% as a yellowish crystals, mp 94–95 °C (from hexane–AcOEt). [Found: C, 75.18; H, 7.87. $C_{17}H_{21}NO_2$ requires: C, 75.25; H, 7.80%.] ν_{max} (KBr) 3286, 1643, 1569, 1460, 1410, 1360, 1172, 1126, 1011, 778, 716, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.41 (1H, m, H_{Ar}), 7.30–7.33 (1H, m, H_{Ar}), 7.22–7.25 (2H, m, H_{Ar}), 6.37 (1H, br s, N*H*), 5.85 (1H, d, *J* 3.0 Hz, 3-H_{fur}), 5.83 (1H, d, *J* 3.0 Hz, 4-H_{fur}), 4.08 (2H, s, CH_2), 2.93 (3H, d, *J* 4.8 Hz, *Me*), 1.23 (9H, s, *t-Bu*).

4.6. 3-(4,4-Dimethyl-3-oxopentyl)-2-methylisoquinolin-1(2*H*)-one (11)

Isoquinolone **11** was obtained analogous to **4a–h** within 10 min. Yield 1.84 g, 68% as a yellowish crystals, mp 98–99 °C (from hexane–AcOEt). [Found: C, 75.31; H, 7.88. $C_{17}H_{21}NO_2$ requires: C, 75.25; H, 7.80%.] ν_{max} (KBr) 2954, 1708, 1647, 1596, 1079, 993, 822, 756, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.34–8.37 (1H, m, H_{Ar}), 7.54–7.59 (1H, m, H_{Ar}), 7.37–7.41 (2H, m, H_{Ar}), 6.29 (1H, s, =C*H*), 3.60 (3H, s, *Me*), 2.92–2.97 (2H, m, CH_2), 2.83–2.88 (2H, m, CH_2), 1.17 (9H, s, *t-Bu*); δ_C (75 MHz, $CDCl_3$) 213.4, 163.5, 142.4, 136.4, 132.1, 127.8, 126.1, 125.2, 124.3, 104.8, 44.3, 35.1, 30.7, 27.7, 26.4 (3C); MS: *m/z* (%) 272 (M^++1, 6), 271 (M^+, 23), 187 (25), 186 (100), 172 (22), 142 (11), 89 (24).

4.7. General procedure for the synthesis of compounds 4a, 13b–f from 12a–f

A mixture of isochromones **12a–f** (0.01 mol) and formamide (45 cm^3) was refluxed until disappearance of the starting compound (25–60 min). Resulted solution was poured into water. The precipitate was filtered off and recrystallized from the mixture of EtOH–1,4-dioxane (1:5). We failed to display ^{13}C NMR spectra of compounds **13b–d** due to their low solubility.

4.7.1. 2,4-Dimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (4a). Yield 2.35 g, 85%, physical and spectral properties were identical to compound synthesized by amide **2a** recyclization.

4.7.2. 10-Chloro-2,4-dimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (13b). Yield 2.59 g, 83.3% as a colorless powder, mp >310 °C (decomp.) (from EtOH–1,4-dioxane). [Found: C, 69.40; H, 4.50. $C_{18}H_{14}ClNO_2$ requires: C, 69.35; H, 4.53%.] ν_{max} (KBr) 1656, 1603, 1472, 1342, 899, 819; δ_H (300 MHz, DMSO) 11.72 (1H, s, N*H*), 8.38 (1H, d, *J* 8.9 Hz, H_{Ar}), 8.18 (1H, d, *J* 2.2 Hz, H_{Ar}), 7.77 (1H, dd, *J* 2.2, 8.9 Hz, H_{Ar}), 6.47 (1H, s, H_{fur}), 5.35 (1H, t, *J* 6.5 Hz, =C*H*), 2.91 (2H, d, *J* 6.5 Hz, CH_2), 2.45 (3H, s, *Me*), 1.98 (3H, s, *Me*); MS: *m/z* (%) 313/311 (M^+, 34/100), 310 (30), 298 (29), 297 (17), 296 (86).

4.7.3. 10-Bromo-2,4-dimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (13c). Yield 3.05 g, 85.6% as a colorless powder, mp >310 °C (decomp.) (from EtOH–1,4-dioxane). [Found: C, 65.59; H, 3.42. $C_{18}H_{14}BrNO_2$ requires: C, 60.69; H, 3.96%.] ν_{max} (KBr) 1654, 1601, 1469, 1342, 902, 818 cm^{-1}; δ_H (300 MHz, DMSO) 11.78 (1H, s, N*H*), 8.33 (1H, d, *J* 2.3 Hz, H_{Ar}), 8.31 (1H, d, *J* 8.9 Hz, H_{Ar}), 7.88 (1H, dd, *J* 2.3, 8.9 Hz, H_{Ar}), 6.47 (1H, s, H_{fur}), 5.35 (1H, t, *J* 6.4 Hz, =C*H*), 2.91 (2H, d, *J* 6.4 Hz, CH_2), 2.45 (3H, s, *Me*), 1.98 (3H, s, *Me*); MS: *m/z* (%) 357/355 (M^+, 100/100), 356 (48), 354 (28), 343 (16), 342(74), 341 (17), 340 (73).

4.7.4. 10-Iodo-2,4-dimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (13d). Yield 3.52 g, 87.4% as a colorless powder, mp >310 °C (decomp.) (from EtOH–1,4-dioxane). [Found: C, 53.55; H, 3.47. $C_{18}H_{14}INO_2$ requires: C, 53.62; H, 3.50%.] ν_{max} (KBr) 3419, 2911, 1650, 1611, 1468, 818, 729, 651 cm^{-1}; δ_H (200 MHz, DMSO) 11.74 (1H, s, N*H*), 8.53 (1H, d, *J* 1.8 Hz, H_{Ar}), 8.15 (1H, d, *J* 8.7 Hz, H_{Ar}), 8.02 (1H, dd, *J* 1.8, 8.7 Hz, H_{Ar}), 6.45 (1H, s, H_{fur}), 5.35 (1H, t, *J* 6.5 Hz, =C*H*), 2.90 (2H, d, *J* 6.5 Hz, CH_2), 2.45 (3H, s, *Me*), 1.98 (3H, s, *Me*); MS: *m/z* (%) 404 (M^++1, 20), 403 (M^+, 100), 402 (14), 389 (10), 388 (49).

4.7.5. 10-Methoxy-2,4-dimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (13e). Yield 2.50 g,

81.3% as a colorless powder, mp >310 °C (decomp.) (from EtOH–1,4-dioxane). [Found: C, 74.34; H, 5.51. $C_{19}H_{17}NO_3$ requires: C, 74.25; H, 5.58%.] ν_{max} (KBr) 1651, 1542, 1486, 1439, 1357, 1287, 1237, 1200, 1102, 1036, 912, 827 cm^{-1}; δ_H (200 MHz, DMSO) 11.55 (1H, s, N*H*), 8.32 (1H, d, *J* 9.1 Hz, H_{Ar}), 7.69 (1H, d, *J* 2.9 Hz, H_{Ar}), 7.37 (1H, dd, *J* 2.9, 9.1 Hz, H_{Ar}), 6.44 (1H, s, H_{fur}), 5.35 (1H, t, *J* 6.6 Hz, =C*H*), 3.87 (3H, s, O*Me*), 2.90 (2H, d, *J* 6.6 Hz, CH_2), 2.45 (3H, s, *Me*), 1.97 (3H, s, *Me*); δ_C (75 MHz, DMSO, 50 °C) 161.3, 157.1, 149.6, 147.7, 132.3, 130.8, 128.7, 125.7, 125.5, 124.8, 121.7, 115.7, 107.7, 105.4, 103.3, 55.0, 30.0, 19.6, 13.0; MS: *m*/*z* (%) 308 (M^++1, 21), 307 (M^+, 100), 306 (26), 293 (17), 292 (79).

4.7.6. 10,11-Dimethoxy-2,4-dimethylfuro[2′,3′:3,4]cyclohepta[1,2-*c*]isoquinolin-8(6*H*)-one (13f). Yield 2.71 g, 80.5% as a colorless powder, mp >310 °C (decomp.) (from EtOH–1,4-dioxane). [Found: C, 71.17; H, 5.60. $C_{20}H_{19}NO_4$ requires: C, 71.20; H, 5.68%.] ν_{max} (KBr) 1665, 1616, 1511, 1380, 1263, 1216, 1171, 1105, 872, 786 cm^{-1}; δ_H (200 MHz, DMSO) 11.48 (1H, s, N*H*), 7.87 (1H, s, H_{Ar}), 7.64 (1H, s, H_{Ar}), 6.45 (1H, s, H_{fur}), 5.34 (1H, t, *J* 6.7 Hz, =C*H*), 3.91 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 2.89 (2H, d, *J* 6,7 Hz, CH_2), 2.45 (3H, s, *Me*), 1.98 (3H, s, *Me*); δ_C (75 MHz, DMSO, 50 °C) 160.9, 152.9, 149.4, 147.7, 133.1, 130.8, 130.1, 124.6, 118.1, 115.6, 107.4, 105.3, 105.1 (2C), 103.1, 55.2, 55.1, 30.1, 19.6, 12.9; MS: *m*/*z* (%) 338 (M^++1, 23), 337 (M^+, 100), 336 (22), 323 (15), 322 (64).

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19. Crystal data of compound **4h**: monoclinic, space group $P2(1)/c$; a=15.123(3), b=5.952(1), c=21.231(4) Å, α=90°, β=97.34(3)°, γ=90°, V=1895.4(6) Å^3, Z=4, D_{calcd}=1.288 g/cm^3, μ(Mo Kα)=0.081 mm^{-1}, 3750 reflections measured, 3618 unique (R_{int}=0.0321), which were used in all calculations. The final $wR(F_2)$ was 0.0718 (all data). Crystallographic data (excluding structural factors) for the structure in this article have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 632893. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uc]. Each request should be accompanied by the complete citation of this paper.
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