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Palladium catalyzed stereoselective synthesis of 3-(anilinoarylmethylene)-2-oxindoles as Hesperadin analogoues

Morteza Bararjanian [a], Saeedeh Hosseinzadeh [a], Saeed Balalaie [a,*], Hamid Reza Bijanzadeh [b]

[a] Peptide Chemistry Research Center, K.N. Toosi University of Technology, P.O. Box 15875-4416 Tehran, Iran
[b] Department of Chemistry, Tarbiat Modares University, P.O. Box 141115-175 Tehran, Iran

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Dedicated to Professor Abbas Shafiee on the occasion of his 70th birthday

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ABSTRACT

Potentially bioactive 3-(anilinoarylmethylene)-2-oxindoles as Hesperadin analogoues have been synthesized via a two-step procedure: (a) an Ugi-4MCR and (b) reaction of the Ugi adduct with aniline in the presence of a palladium catalyst via domino Heck/Buchwald reaction. In all cases, a single isomer with the *Z*-configuration was obtained in good to high yields.

1. Introduction

Oxindoles occupy a key place among the various classes of heterocyclic organic compounds[1] that possess a common basic framework in natural products[2] and pharmaceutically active compounds.[3] Tetrasubstituted 3-methylene-2-oxindoles bearing an exocyclic double bond have shown promising biological activity. Amongst them, 3-(aminomethylene)-2-oxindoles have recently captured attention due to the utility of such structure in the development of biologically active compounds and also new drugs.[2]

The small molecule Hesperadin, is one notable 3-(anilinoarylmethylene)-2-oxindole that has recently been identified as a Aurora B kinase inhibitor themselves a family of mitotic serine/threonine kinases. They are frequently over-expressed in human tumors and also in cancer cells. Accordingly, Aurora kinase is an attractive target and their small molecule inhibitors have received much attention, especially in targeted cancer therapies.[4–7] Hesperadin and related inhibitors, containing an aryl-substituted enamine linkage, is being developed by Boehringer Ingelheim Pharma.[4,8]

Other interesting derivatives similar to Hesperadin are compound A,[9] BIBF 1000,[9] and BIBF 1120.[9,10,11] These are tumor angiogenesis inhibitors. They are in clinical trials for nonsmall cell lung cancer and other tumor types.[9,10] (Fig. 1)

As a result, the development of a new approach for the synthesis of 3-(anilinoarylmethylene)-2-oxindoles is a highly demanded and considerable challenge for the synthetic chemists. Significant effort has been devoted to the development of efficient methods for the stereoselective synthesis of these Hesperadin analogoues. The most straightforward routes to synthesizing this family of type **A** involves the reaction of aniline derivatives with two compounds **B** and **E** (Scheme 1). Condensation of oxindoles **C** with activated acyl derivatives or aryl ortho-esters[12] and also intramolecular arylation of β-keto amides **D** using copper catalysts[13] are two approaches for the synthesis of 3-acyl-oxindoles **B**. Another class of potential precursors to oxindoles of type **A** are 3-(chloromethylene)oxindoles **E**, which have been prepared by: chloropalladation–carbonylation of 2-alkynanilines **F** (cat. $PdCl_2$, $CuCl_2$ in CO atmosphere)[14] or by Iron trichloride-promoted cationic cyclization of 2-alkynylaryl isocyanates **G**,[15] has also been described.

In continuation of our research program to find domino reactions[16] and in view of the interesting biological activities of Hesperadin family in addition to some drawbacks in some of the reported methods, such as lack of generality, limited functional group tolerance, multistep synthesis sequences, and harsh condition, we were motivated to utilize a two-step procedure for stereoselective synthesis of Hesperadin analogoues.

* Corresponding author. E-mail address: Balalaie@kntu.ac.ir (S. Balalaie).

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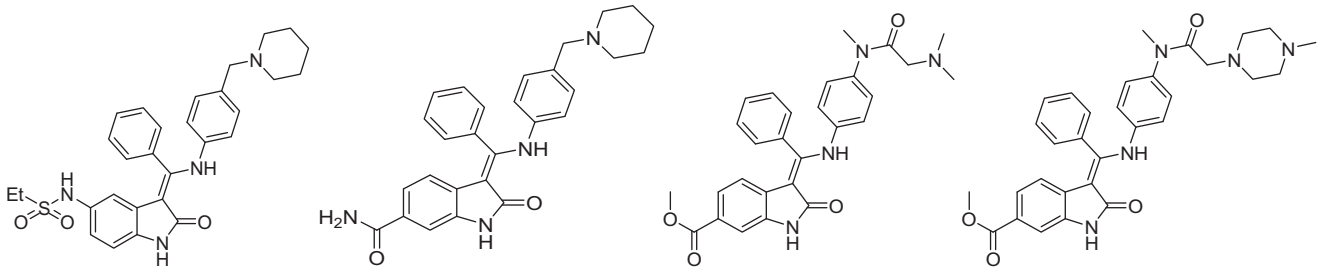
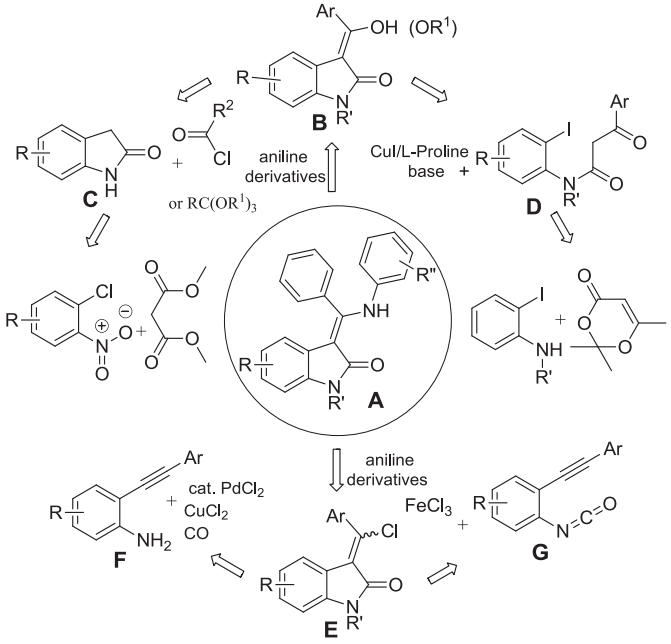
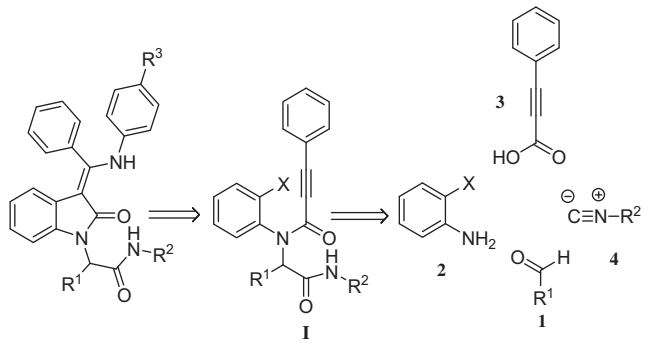


Fig. 1. Biologically active 3-(anilinoarylmethylene)-2-oxindoles.



Scheme 1. Routes and starting materials to 3-(anilinoarylmethylene)-2-oxindoles.

In our retrosynthetic analysis, the formation of the exocyclic double bond in 3-(anilinoarylmethylene)-2-oxindoles was investigated by ring-closure procedure of *N*-substituted 2-alkynamides **I** resulting from the four-component reaction of aldehydes **1**, 2-haloanilines **2**, phenyl propiolic acid **3**, and isocyanides **4** using Pd catalyst (Scheme 2).



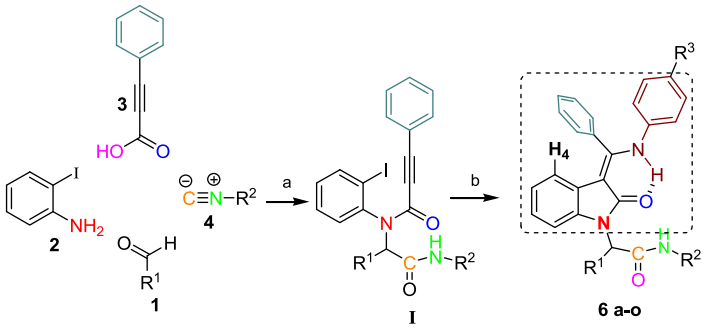
Scheme 2. Retrosynthetic pathway for the synthesis of 3-(anilinoarylmethylene)-2-oxindoles.

To further exploit the generality of the post-functionalization of catalytic multicomponent reaction (MCR) sequences, herein we wish to report a new procedure for the conversion of Ugi 4-MCR intermediate **I** into 3-(anilinoarylmethylene)-2-oxindoles relying on the palladium-catalyzed cyclization reaction of intermediate **I** with aniline derivatives, which products 3-(anilinoarylmethylene)-2-oxindoles (Scheme 3).

2. Results and discussions

Many methods have been developed by chemists in order to facilitate the synthesis of complex natural products.[17] Considering these points, multicomponent reactions through a sequential addition procedure encompass a very broad scope of synthetic transformations. In particular, the combination of structural and functional diversity has initiated the quest of diversity oriented synthesis. Designing molecules, which are capable of reacting in tandem Heck/amination additions across alkynes for the synthesis of heterocycles is an interesting subject in organic chemistry.[18] The Ugi four-component reaction can be used to assemble a complex product from simple starting materials in one step with several advantages, such as wide application scope, high variability, generating multifunctional adducts, and carrying out post-transformation. Several post-transformations have been reported using Ugi products, such as cyclocondensation,[19] radical cyclization,[20] S_NAr,[21] and S_N2 reactions[22]; in all cases various cyclic scaffolds were obtained. The combination of rich and diverse palladium catalyzed chemistry with the Ugi reaction has also been investigated.[23] A number of medicinally relevant heterocycles were synthesized using a combination of Ugi reaction product with Heck reaction, N-arylation, C-arylation of benzylic carbon, the C–H functionalization, the Suzuki–Miyaura reaction, and Sonogashira coupling on the properly functionalized Ugi adducts.[24]

In this approach, simple starting materials selected to generate *N*-substituted-2-alkynamides **I**, which could be synthesized via four-component reactions of benzaldehydes **1**, 2-iodoaniline **2**, phenyl propiolic acid **3**, and isocyanides **4**. We were interested in using the Ugi adduct, which contained an alkyne and also 2-haloaryl moieties to form 3-(anilinoarylmethylene)-2-oxindoles. The reaction of intermediate **I** with aniline derivatives in the presence of $Pd(OAc)_2$ (5 mol %), Cs_2CO_3 leads to form products (**6a**–**o**) in good to high yields (59–96%). The results are summarized in Table 1. The optimization of the reaction conditions was carried out for the synthesis of compound **6g** as a model substrate. Firstly, the Ugi-4MCR product from the reaction of benzaldehyde, 2-iodoaniline, phenylpropiolic acid, and *tert*-butyl isocyanide in MeOH, which led to *N*-substituted-2-alkynamide **Ig** was chosen as an intermediate to screen for the second step (domino Heck/Buchwald coupling reaction). The structure of compound **Ig** was confirmed according to the spectral data. In this approach, $Pd(OAc)_2$ as the catalyst, several bases and phosphine ligands were examined to set up standard reaction conditions for the addition of aniline to **Ig** in the presence of base. K_2CO_3, Cs_2CO_3, and NEt_3 were used as bases in the same conditions and the best results were obtained using Cs_2CO_3, whereas PPh_3 and tri(2-furyl)phosphine as



Scheme 3. Stereoselective synthesis of 3-(anilinoarylmethylene)-2-oxindoles. (a) MeOH, rt, 24 h. (b) 5 mol % $Pd(OAc)_2$, 10 mol % *rac*-BINAP, 2 equiv Cs_2CO_3, aniline derivatives, toluene, reflux.

ligands led to low yields of the desired product, *rac*-BINAP as ligand gave the desired product with good yield.

It seems that the existence of aliphatic substituent in the structure of the products could add the lipophilicity as well as high permeability of the target compounds. To achieve this goal, some aliphatic aldehydes were used. As a result, the yield of the products improved with aliphatic aldehydes as compared to aromatic aldehydes.

The structures of the products **6a**–**o** were characterized using as a single Z-stereo isomer in all cases. The *Z*-configuration of the product was indicated by the signal at δ 5.98–6.08 ppm for the H-4 oxindole proton. This unusual chemical shift is related to anisotropy of phenyl ring. Also, The –NH protons are deshielded and the chemical shifts were observed at 11.86–12.13 ppm. This result was not surprising due to the intramolecular hydrogen bond that can exist between the amino group and the carbonyl group in *Z*-stereo isomer.[15,25]

Our control experiments indicated that this reaction proceeds by two steps, namely: (i) Ugi 4-MCR between aldehydes, 2-iodoaniline, phenylpropiolic acid, and isocyanides leading to *N*-sub stituted-2-alkynamides **I** (ii) Heck carbocyclization/Buchwald coupling of intermediates **I** with aniline derivatives as a domino insertion, coupling sequence to form the 3-(anilinoarylmethylene)-2-oxindoles **6a**–**o**. The proposed mechanism is shown in Scheme 4.

According to the known palladium chemistry, the reaction procedure could be categorized, respectively, as follows: (1) oxidative addition of haloarene **I** to Pd(0) generated Pd(II) species **H** (2) insertion reaction to alkyne moiety and formation of intermediate **J** (Carbopalladation) (3) amination with aniline derivatives and subsequent (4) finally, reductive elimination to afford the products **6a**–**o** with concurrent regeneration of Pd(0) species.

3. Conclusion

In conclusion, 3-(anilinoarylmethylene)-2-oxindoles as Hesperadin analogoues were stereoselectively synthesized through palladium-catalyzed domino Heck/Buchwald reaction with Ugi-4MCR adduct. In all of these compounds, a subtle interplay between steric requirements, polarity and hydrogen-binding capability seemed to be decisive for good potency. Also, suggesting that lipophilic substituents on the indolinone core, such as amido moiety with the ability to form additional hydrogen bond represented the best combination. High bond forming efficiency (BFE), good to high yields, stereoselective synthesis with diversity oriented synthesis (DOS), which could be used in combinatorial chemistry are advantages of this process.

4. Experimental section

4.1. General

Commercially available materials were used without further purification. Melting points were determined on an *Electrothermal 9100* apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR FTLA 2000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on Bruker DRX-500 AVANCE spectrometer at 500 MHz for ^{1}H NMR, and 125 MHz for ^{13}C NMR. $CDCl_3$ was used as solvent. HRMS was recorded on Mass-ESI-POS (Apex Qe-FT-ICR instrument) spectrometer.

4.2. General procedure for the synthesis of *N*-substituted-2-alkynamides Ia–o

2-Iodoaniline (219 mg, 1 mmol), aldehyde (1 mmol), and MeOH (5 mL) were stirred for 30 min. Then, phenyl propiolic acid (146 mg, 1 mmol) and, after 15 min, isocyanide (1 mmol) were added and the mixture was stirred for 24 h. The progress of reaction was monitored by TLC (eluent hexane/ethyl acetate 5:1). The mixture was washed with saturated $NaHCO_3$ (30 mL) and was extracted with ethyl acetate (3×20 mL). Organic phase was dried with Na_2SO_4. The solvent was removed under reduced pressure.

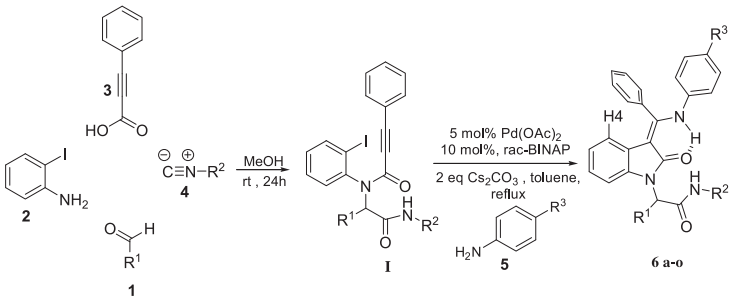
*4.2.1. N-((tert-Butylcarbamoyl)(phenyl)methyl)-N-(2-iodophenyl)-3-phenylpropiolamide (**Ig**).* Compound **Ig** (0.445 g, 83%) as a white solid; mp 191–192 °C; R_f (25% EtOAc/hexane) 0.75; ν_{max} (KBr) 3427, 2204, 1647, 1625, 1556; δ_H (300 MHz, $CDCl_3$) (mixture of two rotamers (87:13)) 1.30 (9H, s, 3CH$_3$ of *t*-Butyl (minor)), 1.35 (9H, s, 3CH$_3$ of *t*-Butyl (major)), 5.40 (1H, s, CH (minor)), 5.63 (1H, br s, NH (major)), 5.90 (1H, s, CH (major)), 6.10 (1H, br s, NH (minor)), 6.90 (1H, td, *J* 7.7, 1.6 Hz, Ar (major)), 7.0–7.6 (20H, m m, Ar mixture of two rotamers), 7.62 (1H, dd, *J* 8.0, 1.4 Hz, Ar (major)), 7.86 (1H, dd, *J* 8.0, 1.4 Hz, Ar (minor)), 8.03 (1H, dd, *J* 9.0, 1.6 Hz, Ar (major)); δ_C (75 MHz, $CDCl_3$) (mixture of two rotamers) 28.6, 29.7, 51.8, 51.8, 60.4, 65.5, 69.0, 76.6, 82.9, 90.8, 91.4, 102.8, 104.2, 120.2, 120.3, 127.9, 128.3, 128.3, 128.6, 128.7, 128.8, 129.2, 129.9, 129.9, 130.0, 130.1, 131.3, 132.1, 132.5, 132.6, 133.2, 135.5, 138.9, 139.4, 141.7, 144.7, 155.0, 155.4, 166.8, 168.4; HRMS (FAB$^+$): MH$^+$ found 537.1011. $C_{27}H_{26}IN_2O_2$ requires 537.1039.

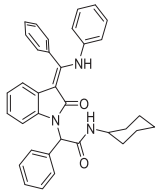
4.3. General procedure for the synthesis of 3-(anilinoarylmethylene)-2-oxindoles 6a–o

The Ugi adduct was added to a flask, which contain toluene (50 mL), $Pd(OAc)_2$ (11 mg, 0.05 equiv), cesium carbonate (652 mg, 2 mmol), *rac*-BINAP (62 mg, 0.1 equiv), and aniline derivatives (2 mmol). The mixture was heated under reflux condition for 7 h. After cooling to room temperature, the reaction mixture was washed with brine (2×30 mL) and organic phase was collected. The combined organic layers were dried with sodium sulfate, concentrated to dryness in vacuo, and purification by column chromatography on silica gel (hexane/ethyl acetate 10:3) to give **6a**–**o** with 59–96%.

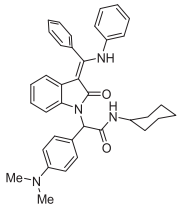
*4.3.1. 2-((Z)-3-((Phenylamino(phenyl)methylene)-2-oxindolin-1-yl)-N-cyclohexyl-2-phenylacetamide (**6a**).* Compound **6a** (0.411 g, 80%) as a yellow solid; mp 255 °C (decomposed); R_f (25% EtOAc/hexane)

Table 1
Synthesis of 3-(anilinoarylmethylene)-2-oxindoles

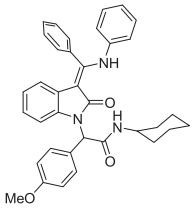




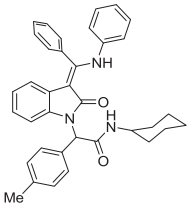
6a (80% yield*)



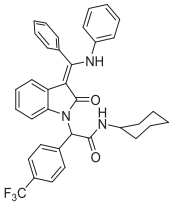
6b (79% yield)



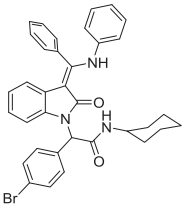
6c (87% yield)



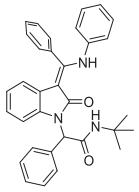
6d (86% yield)



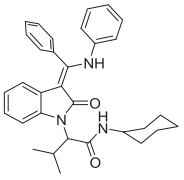
6e (59% yield)



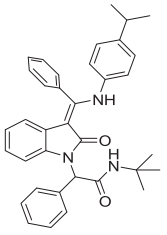
6f (79% yield)



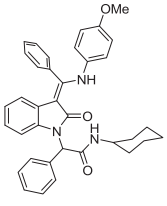
6g (83% yield)



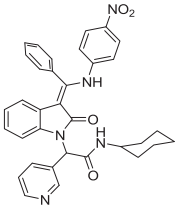
6h (92% yield)



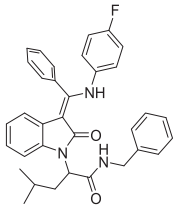
6i (89% yield)



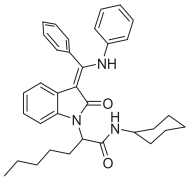
6j (85% yield)



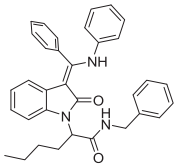
6k (84% yield)



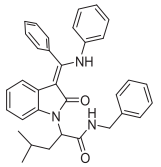
6l (96% yield)



6m (91% yield)

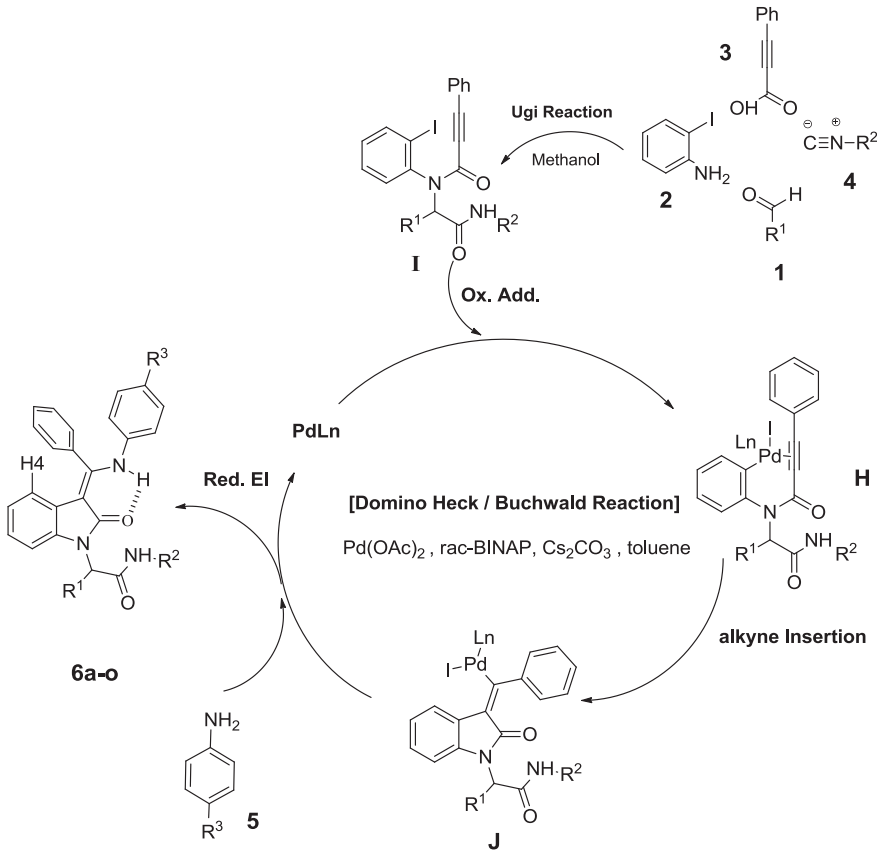


6n (89% yield)



6o (96% yield)

*In all cases, the yields are isolated yield for the final step.



Scheme 4. Possible mechanism for the synthesis of 3-(anilinoarylmethylene)-2-oxindoles.

0.42; ν_{max} (KBr) 3415, 3302, 1684, 1627 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.14–1.98 (10H, m, 5C$\underline{H}_2$ of cyclohexyl), 3.92–3.93 (1H, m, C$\underline{H}$ of cyclohexyl), 6.02 (1H, d, *J* 7.8 Hz, Ar–$\underline{H}_4$), 6.34 (1H, s, NC$\underline{H}$CO), 6.50 (1H, d, *J* 7.7 Hz, CONH$\underline{C}$H), 6.63–6.67 (1H, m, Ar), 6.78 (2H, d, *J* 8.1 Hz, Ar), 6.90–6.94 (2H, m, Ar), 6.99 (1H, t, *J* 7.4 Hz, Ar), 7.11 (2H, t, *J* 7.7 Hz, Ar), 7.27–7.56(10H, m, Ar), 11.95 (1H, s, N$\underline{H}$Ph); δ_C 24.7, 24.8, 25.5, 32.7, 32.8, 48.7 (*C*-cyclohexyl), 59.1 (N$\underline{C}$HCO), 97.1, 110.2, 118.8, 121.2, 123.1, 123.5, 124.1, 124.5, 128.0, 128.6, 128.8, 129.4, 130.1, 133.0, 135.2, 136.4, 138.7, 157.4, 167.4 (C=O), 169.2 (C=O); HRMS (ESI): MH^+ found 528.2655. $C_{35}H_{34}N_3O_2$ requires 528.2657.

*4.3.2. 2-((Z)-3-((Phenylamino(phenyl)methylene)-2-oxindolin-1-yl)-N-cyclohexy-2-(4-(dimethylamino)phenyl)-acetamide (**6b**).* Compound **6b** (0.451 g, 79%) as a yellow solid; mp 236 °C (dec); R_f (25% EtOAc/hexane) 0.44; ν_{max} (KBr) 3410, 3306, 1681, 1625 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.18–1.97 (10H, m, 5C$\underline{H}_2$ of cyclohexyl), 2.94 (6H, s, 2C$\underline{H}_3$), 3.87–3.97 (1H, m, C$\underline{H}$ of cyclohexyl), 5.99 (1H, d, *J* 7.8 Hz, Ar–$\underline{H}_4$), 6.22 (1H, s, NC$\underline{H}$CO), 6.41 (1H, d, *J* 7.9 Hz, CONH$\underline{C}$H), 6.61–6.64 (1H, m, Ar), 6.69 (2H, d, *J* 8.7 Hz, Ar), 6.77(2H, d, *J* 7.9 Hz, Ar), 6.89–6.94 (2H, m, Ar), 6.97 (1H, t, *J* 7.3 Hz, Ar), 7.10 (2H, t, *J* 7.7 Hz, Ar), 7.31 (2H, d, *J* 8.7 Hz, Ar), 7.43–7.53 (5H, m, Ar), 11.97 (1H, s, N$\underline{H}$Ph); δ_C (125 MHz, $CDCl_3$) 24.8, 25.5, 32.8, 32.9 (*C*-cyclohexyl), 40.4 (2$\underline{C}H_3$), 48.6 (*C*-cyclohexyl), 59.0 (N$\underline{C}$HCO), 97.4, 109.1, 110.2, 112.5, 118.8, 119.0, 120.8, 120.9, 122.7, 123.0, 123.1, 123.4, 123.6, 124.1, 124.3, 128.7, 128.8, 128.9, 129.0, 129.3, 130.0, 133.1, 136.8, 138.9, 150.2, 157.0, 168.0 (C=O), 169.3 (C=O); HRMS (ESI): MH^+ found 571.3078. $C_{37}H_{39}N_4O_2$ requires 571.3079.

*4.3.3. 2-((Z)-3-((Phenylamino)(phenyl)methylene)-2-oxindolin-1-yl)-N-cyclohexyl-2-(4-methoxyphenyl)acetamide (**6c**).* Compound **6c** (0.484 g, 87%) as a yellow solid; mp 211 °C (dec); R_f (25% EtOAc/hexane) 0.33; ν_{max} (KBr) 3410, 3281, 1684, 1622 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.13–1.98 (10H, m, 5C$\underline{H}_2$ of cyclohexyl), 3.80 (3H, s, OC$\underline{H}_3$), 3.91–3.92 (1H, m, C$\underline{H}$ of cyclohexyl), 6.00 (1H, d, *J* 7.6 Hz, Ar–$\underline{H}_4$), 6.27 (1H, s, NC$\underline{H}$CO), 6.44 (1H, d, *J* 7.9 Hz, CONH$\underline{C}$H), 6.63–6.66 (1H, m, Ar), 6.77 (2H, d, *J* 8.1 Hz, Ar), 6.87–6.93 (4H, m, Ar), 6.99 (1H, t, *J* 7.5 Hz, Ar), 7.11 (2H, t, *J* 7.7 Hz, Ar), 7.36 (2H, d, *J* 8.7 Hz, Ar), 7.43–7.55 (5H, m, Ar), 11.95 (1H, s, N$\underline{H}$ph); δ_C (125 MHz, $CDCl_3$) 24.7, 25.5, 32.8, 32.9, 48.7 (*C*-cyclohexyl), 55.3 (O$\underline{C}H_3$), 58.6 (N$\underline{C}$HCO), 97.2, 110.1, 114.1, 118.8, 121.1, 123.1, 123.5, 124.1, 124.4, 127.3, 128.8, 129.3, 129.4, 130.1, 133.0, 136.4, 138.7, 157.3, 159.2, 167.6 (C=O), 169.2 (C=O); HRMS (ESI): MH^+ found 558.2763. $C_{36}H_{36}N_3O_3$ requires 558.2763.

*4.3.4. 2-((Z)-3-((Phenylamino)(phenyl)methylene)-2-oxindolin-1-yl)-N-cyclohexyl-2-p-tolylacetamide (**6d**).* Compound **6d** (0.465 g, 86%) as a yellow solid; mp 214 °C (dec); R_f (25% EtOAc/hexane) 0.42; ν_{max} (KBr) 3415, 3302, 1689, 1632 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.14–1.97 (10H, m, 5C$\underline{H}_2$ of cyclohexyl), 2.33 (3H, s, C$\underline{H}_3$), 3.91–3.93 (1H, m, C$\underline{H}$ of cyclohexyl), 6.01 (1H, d, *J* 7.8 Hz, Ar–$\underline{H}_4$), 6.28 (1H, s, NC$\underline{H}$CO), 6.50, (1H, d, *J* 7.7 Hz, CONH$\underline{C}$H), 6.63–6.67 (1H, m, Ar), 6.77 (2H, d, *J* 8.0 Hz, Ar), 6.92 (2H, d, *J* 4.2 Hz, Ar), 6.99 (1H, t, *J* 7.5 Hz, Ar), 7.11 (2H, t, *J* 7.7 Hz, Ar), 7.15 (2H, d, *J* 7.9 Hz, Ar), 7.31 (2H, d, *J* 7.9 Hz, Ar), 7.44–7.56 (5H, m, Ar), 11.95 (1H, s, N$\underline{H}$Ph); δ_C (125 Hz, $CDCl_3$) 21.1 (C$\underline{H}_3$), 24.6, 24.8, 25.5, 32.7, 32.8, 48.6 (*C*-cyclohexyl), 59.0 (N$\underline{C}$HCO), 97.2, 110.1, 118.8, 121.1, 123.0, 123.1, 123.5, 124.1, 124.4, 127.9, 128.7, 128.8, 129.4, 130.1, 132.2, 133.0, 136.5, 137.7, 138.7, 157.3, 167.5 (C=O), 169.3 (C=O); HRMS (ESI): MH^+ found 542.2812. $C_{36}H_{36}N_3O_2$ requires 542.2812.

4.3.5. 2-((Z)-3-((Phenylamino)(phenyl)methylene)-2-oxindolin-1-yl)-N-cyclohexyl-2-(4-(trifluoromethyl)phenyl)acetamide

(**6e**). Compound **6e** (0.351 g, 59%) as a light-red solid; mp 100 °C; R_f (25% EtOAc/hexane) 0.45; ν_{max} (KBr) 3410, 3286, 1694, 1632 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.10–1.93 (10H, m, $5CH_2$ of cyclohexyl), 3.81–3.95 (1H, m, CH of cyclohexyl), 6.03 (1H, d, *J* 7.8 Hz, Ar–H_4), 6.39 (1H, s, NCHCO), 6.57 (1H, d, *J* 7.5 Hz, CONHCH), 6.69 (1H, t, *J* 7.6 Hz, Ar), 6.78 (2H, d, *J* 8.1 Hz, Ar), 6.88(1H, d, *J* 7.9 Hz, Ar), 6.94 (1H, t, *J* 7.8 Hz, Ar), 7.01 (1H, t, *J* 7.4 Hz, Ar), 7.12 (2H, t, *J* 7.8 Hz, Ar), 7.44–7.57 (7H, m, Ar), 7.59 (2H, d, *J* 8.1 Hz, Ar), 11.90 (1H, s, NHPh); δ_C (125 MHz, $CDCl_3$) 24.6, 24.7, 25.4, 29.3, 29.7, 48.9 (*C*-cyclohexyl), 58.3 (NCHCO), 96.7, 110.1, 118.9, 121.6, 123.2, 123.6, 124.1, 124.8, 125.4, 125.5, 128.3, 128.7, 128.8, 128.9, 129.3, 129.4, 130.2, 131.8, 132.7, 135.7, 138.4, 139.1, 158.0, 166.7 (C=O), 169.1 (C=O); HRMS (ESI): MH^+ found 596.2525. $C_{36}H_{33}F_3N_3O_2$ requires 596.2526.

*4.3.6. 2-((Z)-3-((Phenylamino)(phenyl)methylene)-2-oxindolin-1-yl)-N-cyclohexyl-2-(4-bromophenyl) acetamide (**6f**).* Compound **6f** (0.478 g, 79%) as a yellow solid; mp 186 °C; R_f (25% EtOAc/hexane) 0.55; ν_{max} (KBr) 3410, 3291, 1689, 1627 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.10–1.95 (10H, m, $5CH_2$ of cyclohexyl), 3.82–3.97 (1H, m, CH of cyclohexyl), 6.02 (1H, d, *J* 7.8 Hz, Ar–H_4), 6.29 (1H, s, NCHCO), 6.53 (1H, d, *J* 7.9 Hz, CONHCH), 6.68 (1H, t, *J* 7.6 Hz, Ar), 6.77 (2H, d, *J* 7.9 Hz, Ar), 6.87 (1H, d, *J* 7.9 Hz, Ar), 6.93 (1H, t, *J* 7.7 Hz, Ar), 7.01 (1H, t, *J* 7.5 Hz, Ar), 7.12 (2H, d, *J* 7.7 Hz, Ar), 7.28 (2H, d, *J* 8.5 Hz, Ar), 7.44–7.57 (7H, m, Ar), 11.91 (1H, s, NHPh); δ_C (125 MHz, $CDCl_3$) 24.7, 24.8, 25.5, 32.8, 48.8 (*C*-cyclohexyl), 58.3 (NCHCO), 96.8, 110.1, 118.9, 121.5, 122.0, 123.2, 123.5, 124.1, 124.7, 128.7, 128.8, 128.9, 129.3, 129.4, 129.7, 130.2, 131.7, 132.8, 134.2, 135.8, 138.5, 157.8, 166.9 (C=O), 169.1 (C=O); HRMS (ESI): MH^+ found 606.1762. $C_{35}H_{33}^{79}BrN_3O_2$ requires 606.1764.

*4.3.7. 2-((Z)-3-((Phenylamino(phenyl)methylene)-2-oxindolin-1-yl)-N-tert-butyl-2-phenylacetamide (**6g**).* Compound **6g** (0.416 g, 83%) as a yellow solid; mp 190 °C; R_f (25% EtOAc/hexane) 0.49; ν_{max} (KBr) 3420, 3302, 1699, 1627 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.39 (9H, s, $3CH_3$ of *t*-Butyl), 6.01 (1H, d, *J* 7.8 Hz, Ar–H_4), 6.26 (1H, s, NCHCO), 6.42 (1H, s, CONHC$(CH_3)_3$), 6.63–6.67 (1H, m, Ar), 6.77 (2H, d, *J* 7.9 Hz, Ar), 6.91 (2H, d, *J* 4.1 Hz, Ar), 6.99 (1H, t, *J* 7.5 Hz, Ar), 7.11 (2H, t, *J* 7.8 Hz, Ar), 7.33–7.56 (9H, m, Ar), 12.00 (1H, s, NHPh); δ_C (125 MHz, $CDCl_3$) 28.6 ($3CH_3$ of *t*-Butyl), 51.8 (C-*t*-Butyl), 59.6 (NCHCO), 97.2, 110.3, 118.8, 121.1, 122.9, 123.1, 123.5, 124.1, 124.4, 127.9, 128.6, 128.7, 128.8, 129.3, 130.1, 132.9, 135.4, 136.5, 138.7, 157.3, 167.5 (C=O), 169.2 (C=O); HRMS (ESI): MH^+ found 502.2499.$C_{33}H_{32}N_3O_2$ requires 502.2501.

*4.3.8. 2-((Z)-3-((Phenylamino(phenyl)methylene)-2-oxindolin-1-yl)-N-cyclohexyl-3-methylbutanamide (**6h**).* Compound **6h** (0.454 g, 92%) as a yellow solid; mp 219 °C (dec); R_f (25% EtOAc/hexane) 0.45; ν_{max} (KBr) 3429, 3304, 1684, 1638 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.79 (3H, d, *J* 6.6 Hz, CH_3CH_3CH), 1.02–1.14 (3H, m, H-cyclohexyl)), 1.17 (3H, d, *J* 6.6 Hz, CH_3CH_3CH), 1.20–1.96 (7H, m, H-cyclohexyl), 2.90–3.15 (1H, m, $CHCH_3CH_3$), 3.72–3.78 (1H, m, CH of cyclohexyl), 4.55 (1H, br s, CONHCH), 5.96 (1H, s, NCHCO), 5.99 (1H, d, *J* 7.8 Hz, Ar–H_4), 6.66 (1H, t, *J* 7.7 Hz, Ar), 6.77 (2H, d, *J* 7.9 Hz, Ar), 6.99 (2H, t, *J* 7.5 Hz, Ar), 7.12 (2H, t, *J* 7.9 Hz, Ar), 7.27 (1H, d, *J* 7.5 Hz, Ar), 7.44–7.55 (5H, m, Ar), 12.00 (1H, s, NHPh); δ_C (125 MHz, $CDCl_3$) 19.3 (CH_3CH_3CH), 20.3 (CH_3CH_3CH), 24.6, 24.7, 25.6 (*C*-cyclohexyl), 27.2 ($CHCH_3CH_3$), 32.8, 48.3 (*C*-cyclohexyl), 74.2 (NCHCO), 97.2, 110.0, 118.7, 121.1, 122.8, 123.6, 123.8, 124.4, 128.8, 128.9, 129.4, 130.1, 132.9, 138.8, 157.3, 168.8 (C=O), 169.6 (C=O); HRMS (ESI): MH^+ found 494.2810.$C_{32}H_{36}N_3O_2$ requires 494.2810.

*4.3.9. 2-((Z)-3-((4-Isopropylphenylamino)(phenyl)methylene)-2-oxindolin-1-yl)-tert-butyl-2-phenyl acetamide (**6i**).* Compound **6i** (0.484 g, 89%) as a yellow solid; mp 135 °C; R_f (25% EtOAc/hexane) 0.62; ν_{max} (KBr) 3410, 3302, 1689, 1622 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.16 (6H, d, *J* 6.9 Hz, CH_3CH_3CH), 1.40 (9H, s, $3CH_3$ of *t*-Butyl), 2.74–2.84 (1H, m, $CHCH_3CH_3$), 5.98 (1H, d, *J* 7.4 Hz, Ar–H_4), 6.23 (1H, s, NCHCO), 6.48 (1H, s, CONHC$(CH_3)_3$), 6.63–6.66 (1H, m, Ar), 6.69 (2H, d, *J* 8.5 Hz, Ar), 6.90–6.92 (2H, m, Ar), 6.96 (2H, d, *J* 8.5 Hz, Ar), 7.30–7.53 (10H, m, Ar), 11.95 (1H, s, NHPh); δ_C (125 MHz, $CDCl_3$), 23.8 (CH_3CH_3CH), 28.7 ($3CH_3$ of *t*-Butyl), 33.4 (CH_3CH_3CH), 51.8 ($CHCH_3CH_3$), 59.6 (NCHCO), 96.7, 110.3, 118.7, 121.1, 122.7, 123.2, 124.2, 126.7, 127.8, 127.9, 128.6, 128.7, 129.3, 130.0, 133.1, 135.4, 136.3, 136.4, 145.1, 157.5, 167.6 (C=O), 169.1 (C=O); HRMS (ESI): MH^+ found 544.2964. $C_{36}H_{38}N_3O_2$ requires 544.2965.

*4.3.10. 2-((Z)-3-((4-Methoxyphenylamino)(phenyl)methylene)-2-oxindolin-1-yl)-N-cyclohexyl-2-phenylacetamide (**6j**).* Compound **6j** (0.474 g, 85%) as a yellow solid; mp 135 °C; R_f (25% EtOAc/hexane) 0.31; ν_{max} (KBr) 3420, 3291, 1684, 1628 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.13–1.95 (10H, m, $5CH_2$ of cyclohexyl), 3.71 (3H, s, OCH_3), 3.90–3.95(1H, m, CH of cyclohexyl), 5.99 (1H, d, *J* 7.8 Hz, Ar–H_4), 6.33 (1H, s, NCHCO), 6.54 (1H, d, *J* 7.9 Hz, CONHCH), 6.63–6.67 (3H, m, Ar), 6.75 (2H, d, *J* 8.9 Hz, Ar), 6.90 (2H, d, *J* 4.0 Hz, Ar), 7.30–7.51 (10H, m, Ar), 11.82 (1H, s, NHPh); δ_C (125 MHz, $CDCl_3$) 24.7, 24.8, 25.5, 32.7, 32.8, 48.7 (*C*-cyclohexyl), 55.3 (OCH_3), 59.1 (NCHCO), 96.1, 110.1, 114.0, 114.8, 116.4, 118.6, 121.1, 123.1, 124.3, 125.2, 127.9,128.0, 128.6, 128.8, 128.9, 129.2, 129.3, 130.0, 131.5, 133.0, 135.3, 136.1, 156.9, 158.3, 167.5 (C=O), 169.2 (C=O); HRMS (ESI): MH^+ found 558.2756. $C_{36}H_{36}N_3O_3$ requires 558.2757.

*4.3.11. 2-((Z)-3-((4-Nitrophenylamino)(phenyl)methylene)-2-oxindolin-1-yl)-N-cyclohexyl-2-(pyridine 3-yl)acetamide (**6k**).* Compound **6k** (0.481 g, 84%) as a light-red solid; mp 140–142 °C; R_f (50% EtOAc/hexane) 0.22; ν_{max} (KBr) 3409, 3215, 1648, 1581 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.11–1.67 (10H, m, $5CH_2$ of cyclohexyl), 3.85–3.95 (1H, m, CH of cyclohexyl), 6.08 (1H, d, *J* 7.8 Hz, Ar–H_4), 6.31 (1H, d, *J* 7.9 Hz, CONHCH), 6.35 (1H, s, NCHCO), 6.68–6.75 (3H, m, Ar), 6.88 (1H, d, *J* 7.9 Hz, Ar), 6.98 (1H, t, *J* 7.8 Hz, Ar), 7.27–7.68 (6H, m, Ar), 7.82 (1H, d, *J* 7.9 Hz, Ar), 7.96 (2H, d, *J* 9.1 Hz, Ar), 8.55 (1H, d, *J* 4.3 Hz, Ar), 8.63 (1H, s, Ar), 12.13 (1H, s, NHPh); δ_C (125 MHz, $CDCl_3$) 24.7, 24.8, 25.3, 32.7, 32.8, 49.1 (*C*-cyclohexyl), 56.4 (NCHCO), 100.4, 110.5, 119.9, 120.7, 122.2, 123.2, 123.4, 124.9, 125.1, 128.5, 130.1, 130.2, 130.8, 131.0, 132.2, 136.2, 136.4, 143.1, 144.9, 149.1, 149.3, 154.8, 166.0 (C=O), 169.2 (C=O); HRMS (ESI): MH^+ found 522.31207. $C_{34}H_{40}N_3O_2$ requires 522.31218.

*4.3.12. 2-((Z)-3-((4-Fluorophenylamino)(phenyl)methylene)-2-oxindolin-1-yl)-N-benzyl-4-methyl pentanamide (**6l**).* Compound **6l** (0.512 g, 96%) as a yellow solid; mp 78–80 °C; R_f (25% EtOAc/hexane) 0.52; ν_{max} (KBr) 3416, 3317, 1680, 1648 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.6 Hz,CH_3CH_3CH), 1.02 (3H, d, *J* 6.6 Hz, CH_3CH_3CH), 1.48–1.51 (1H, m, CH_3CH_3CH), 2.21–2.28 (2H, m, $CHCH_2CH$), 4.46 (2H, d, *J* 5.8 Hz, CH_2Ph), 5.30–5.50 (1H, m, NCHCO), 6.02 (1H, d, *J* 7.8 Hz, Ar–H_4), 6.46–6.67 (1H, m, $CONHCH_2$), 6.70 (1H, t, *J* 7.9 Hz, Ar), 6.75–7.03 (6H, m, Ar), 7.15 (2H, d, *J* 7.0 Hz, Ar), 7.21–7.27 (3H, m, Ar), 7.36 (1H, d, *J* 7.4 Hz, Ar), 7.43–7.55 (4H, m, Ar), 11.86 (1H, s, NHPh); δ_C (125 MHz, $CDCl_3$) 21.8 (CH_3), 23.2 (CH_3), 25.1 (CH_3CH_3CH), 36.9 ($CHCH_2CH$), 43.4 (CH_2Ph), 53.4 (NCHCO), 97.0, 110.0, 115.6 (d, $^2J_{C-F}$ 22.7 Hz), 118.9, 121.3, 123.7, 124.0, 125.2 (d, $^3J_{C-F}$ 8.2 Hz), 127.3, 127.5, 128.5, 128.7, 128.9, 129.4, 130.2, 132.5, 134.6, 135.6, 138.1, 157.7, 159.8 (d, $^1J_{C-F}$ 243.5 Hz), 169.3 (C=O), 170.5 (C=O); HRMS (ESI): MH^+ found 534.2559. $C_{34}H_{33}FN_3O_2$ requires 534.2561.

*4.3.13. 2-((Z)-3-((Phenylamino)(phenyl)methylene)-2-oxindolin-1-yl)-N-cyclohexyl heptanamide (**6m**).* Compound **6m** (0.474 g, 91%) as a yellow solid; mp 117–119 °C; R_f (25% EtOAc/hexane) 0.51; ν_{max} (KBr) 3420, 3327, 1627, 1683 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.83 (3H, t, *J* 7.0 Hz, CH_3CH_2), 0.86–2.41 (18H, m, $CH_3(CH_2)_4$, $5CH_2$ of cyclohexyl), 3.73–3.85 (1H, m, CH of cyclohexyl), 5.10–5.22 (1H, m, NCHCO), 6.02 (1H, d, *J* 7.8 Hz, Ar–H_4), 6.10 (1H, br, CONHCH), 6.67–6.70 (1H, m, Ar), 6.78 (2H, d, *J* 7.8 Hz, Ar), 6.96–7.01 (3H, m, Ar), 7.12 (2H, t, *J* 7.8 Hz, Ar), 7.41–7.57 (5H, m, Ar), 11.98 (1H, s, NHPh); δ_C (125 MHz, $CDCl_3$) 13.9 (CH_3CH_2), 22.4 (CH_3CH_2), 24.7,

24.8, 25.5 (*C*-cyclohexyl), 26.1 ($CH_3CH_2\underline{C}H_2$), 28.1 ($\underline{C}H_2CH_2CH$), 31.4 (*C*-cyclohexyl), 32.8 ($CH_2\underline{C}H_2CH$), 48.5 (*C*-cyclohexyl), 55.4 (N$\underline{C}$HCO), 96.9, 110.0, 118.8, 121.2, 123.0, 123.5, 124.1, 124.5, 128.7, 128.8, 128.9, 129.3, 129.4, 130.1,132.9, 135.6, 138.7, 157.3, 169.2 (C=O), 169.5 (C=O); HRMS (ESI): MH^+ found 522.3121. $C_{34}H_{40}N_3O_2$ requires 522.3122.

*4.3.14. 2-((Z)-3-((Phenylamino)(phenyl)methylene)-2-oxindolin-1-yl)-N-benzyl hexanamide (**6n**).* Compound **6n** (0.458 g, 89%) as a yellow solid; mp 56–59 °C; R_f (25% EtOAc/hexane) 0.52; ν_{max} (KBr) 3417, 3322, 1685, 1627 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0 Hz, $C\underline{H}_3CH_2$), 1.26–2.45 (6H, m, $CH_3(C\underline{H}_2)_3$), 4.46 (2H, d, *J* 6.0 Hz, $C\underline{H}_2Ph$), 5.18–5.25(1H, m, NC$\underline{H}$CO), 6.01 (1H, d, *J* 7.8 Hz, Ar–$\underline{H}_4$), 6.46–6.65 (1H, m, CON$\underline{H}CH_2$), 6.68–6.71 (1H, m, Ar), 6.76 (2H, d, *J* 8.0 Hz, Ar), 6.96–7.01 (2H, m, Ar), 7.11–7.56 (13H, m, Ar), 11.95 (1H, s, N$\underline{H}$Ph); δ_C (125 MHz, $CDCl_3$) 13.9 ($\underline{C}H_3CH_2$), 22.3 ($CH_3\underline{C}H_2$), 28.1 ($CH_3CH_2\underline{C}H_2$), 28.5 ($\underline{C}H_2CH$), 43.5 ($\underline{C}H_2Ph$), 55.3 (N$\underline{C}$HCO), 96.8, 109.9, 118.9, 121.3, 123.0, 123.6, 124.1, 124.5, 127.3, 127.5, 128.5, 128.8, 129.4, 130.1, 132.6, 132.9, 138.1, 138.6,139.3, 157.4, 169.4 (C=O), 170.3 (C=O); HRMS (ESI): MH^+ found 516.2652. $C_{34}H_{34}N_3O_2$ requires 516.2653.

*4.3.15. 2-((Z)-3-((Phenylamino)(phenyl)methylene)-2-oxindolin-1-yl)-N-benzyl-4-methyl pentanamide (**6o**).* Compound **6o** (0.495 g, 96%) as a yellow solid; mp 76 °C; R_f (25% EtOAc/hexane) 0.45; ν_{max} (KBr) 3435, 3280, 1674, 1632 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.6 Hz,CH_3CH_3CH), 1.04 (3H, d, *J* 6.6 Hz, $CH_3C\underline{H}_3CH$), 1.50–1.53 (1H, m, $CH_3CH_3C\underline{H}$), 2.23–2.30 (2H, m, $CHC\underline{H}_2CH$), 4.46 (2H, d, *J* 4.0 Hz, $C\underline{H}_2Ph$), 5.29–5.51 (1H, m, NC$\underline{H}$CO), 6.04 (1H, d, *J* 7.8 Hz, Ar–$\underline{H}_4$), 6.41–6.67 (1H, m, CON$\underline{H}CH_2$), 6.69–6.72 (1H, m, Ar), 6.78 (2H, d, *J* 7.9 Hz, Ar), 6.99–7.04 (3H, m, Ar), 7.12 (2H, t, *J* 7.9 Hz, Ar), 7.17 (2H, d, *J* 6.8 Hz, Ar), 7.21–7.28 (3H, m, Ar), 7.41 (1H, d, *J* 7.5 Hz, Ar), 7.48–7.50 (4H, m, Ar), 11.98 (1H, s, N$\underline{H}$Ph); δ_C (125 MHz, $CDCl_3$) 21.8 ($\underline{C}H_3$), 23.2 ($\underline{C}H_3$), 25.2 ($CH_3CH_3\underline{C}H$), 36.9 ($CH\underline{C}H_2CH$), 43.6 ($\underline{C}H_2Ph$), 53.4 (N$\underline{C}$HCO), 97.0, 110.0, 118.9, 121.3, 123.1, 123.7, 124.2, 124.5, 127.3, 127.5, 128.6, 128.9, 129.4, 130.1, 132.9, 135.7, 138.1, 138.6, 157.4, 169.3 (C=O), 170.6 (C=O); HRMS (ESI): MH^+ found 516.2652. $C_{34}H_{34}N_3O_2$ requires 516.2653.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.02.005.

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