Tetrahedron 67 (2011) 9134–9141

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Pd-catalyzed synthesis of 3-(diarylmethylene)-2-oxindoles and 3-(arylmethylene)-2-oxindoles

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ARTICLE INFO

Article history:
Received 20 May 2011
Received in revised form 25 August 2011
Accepted 20 September 2011
Available online 25 September 2011

Dedicated to Professor M. M. Hashemi on the occasion of his 60th birthday

Keywords:
3-(Diarylmethylene)-2-oxindoles
3-(Arylmethylene)-2-oxindoles
Modified Heck reaction
Palladium catalyst

ABSTRACT

An efficient method for the stereoselective synthesis of 3-(diarylmethylene)-2-oxindoles and 3-(arylmethylene)-2-oxindoles via carbopalladation is described. In this approach, an Ugi-4-component reaction (4-CR) adduct was used as the starting material. A one-pot sequence involving intermolecular carbopalladation C–H activation/C–C bond formation efficiently afforded the oxindole derivatives.

1. Introduction

3-Alkylideneoxindoles are well known to be versatile compounds in synthesis and biology.[1] Some of the *E*- and *Z*-alkylidene-2-oxindoles were found to be promising inhibitors of tyrosine-kinase, such as SU4984,[1a,2] cyclic-dependent protein kinase inhibitors,[3] and antirheumatic agents.[4] Compound **B** (SU11248) is the orally active receptor tyrosine kinase (RTK) inhibitor marketed by Pfizer as Sutent®.[5] Semaxanib (SU5416, **C**) is a related anticancer compound, which passed to phase III clinical trials for use in the treatment of colo-rectal cancer. Meanwhile, *E*-alkylideneoxindoles are important synthetic intermediates to TMC-95A.[6] The cone structure of some 3-methylidene-2-oxinoles is shown in Fig. 1.

Also, some 3-alkenyl-2-oxindole derivatives were separated from natural sources (Fig. 2), which possess different biological activities, such as antipyretic (E),[7] antiviral, detoxifying (G),[8] anti-inflammatory, analgesic properties (H),[9] and some of them are self-germination inhibitors (F).[10]

The existence of tri- or tetra-substituted olefin in the 3-alkylidene-2-oxindole scaffold is important for their biological activitiy.[3,11] A number of related compounds are given in a review article.[12]

Consequently, the synthesis of 2-oxindoles with a tri- or tetra-substituted exocyclic double-bond at the C-3 position is an interesting goal.[13] There are several approaches for the synthesis of 3-arylidene and diarylidene-2-oxindoles, which are summarized in Scheme 1.

The metal-catalyzed domino cyclization of a suitable starting material is an efficient method to construct the oxindole skeleton. In this way, the suitable materials are: amidophosphonates (route a),[13] 2-alkynyl anilines (route b),[14] 2-iodoarylpropynamides (route c),[15] 2-carboamidoaryl triflate (route d).[16] *N*-Substituted-2-alkynamides are both common and suitable starting material for the synthesis of 3-arylidene-2-oxindoles.[15d,17] It was shown that a transition-metal could catalytically activate sp^2 C–H bonds of arenes to form new C–C bonds.[18] Zhu and co-workers have reported an interesting palladium-catalyzed domino N-arylation/carbopalladation/C–H functionalization reaction of arylalkynes with electrophilic aryl iodides to afford five-membered heterocycles.[19] There are two different strategies for the synthesis of 3-alkylidene-2-oxindoles using *N*-substituted-2-alkynamides via arene–alkyne-cyclization, as summarized in Scheme 2.[19e]

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doi:10.1016/j.tet.2011.09.089

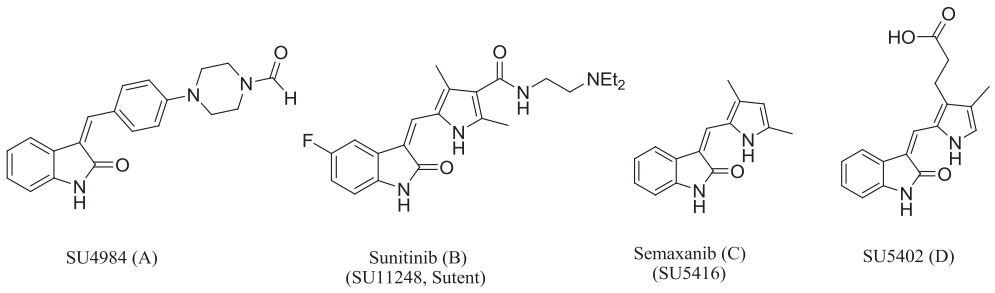


Fig. 1. Representative 3-alkenyl-oxindoles.

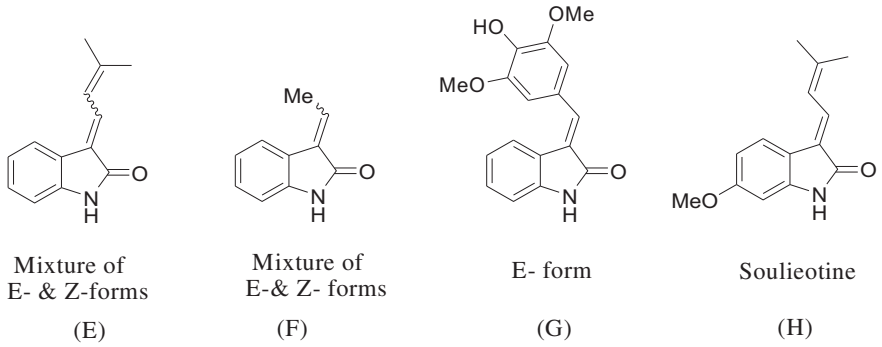
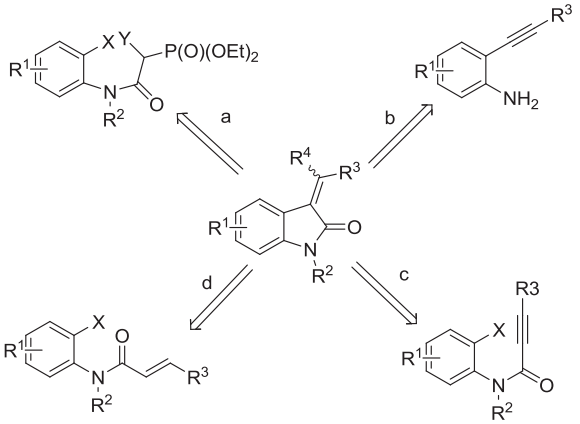
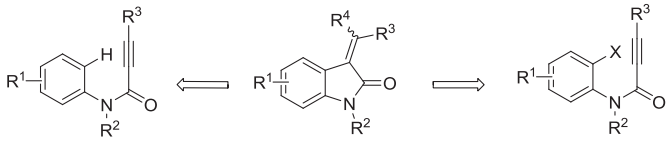


Fig. 2. The structures of some natural 3-arylidene-2-oxindoles.



Scheme 1. Some approaches for the synthesis of 3-arylidene-2-oxindoles.

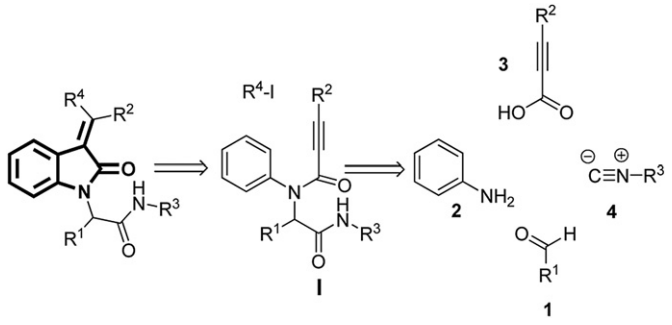


Scheme 2. Two different strategies for the synthesis of 3-alkylidene-2-oxindoles.

In these approaches two different three-component variants were used for the stereoselective synthesis of unsymmetrically substituted 3-diarylmethylene-2-oxindoles, derived from terminal alkynes and two aryl iodides using an in situ Sonogashira cross-coupling.[19d]

The number of aryl groups and their stereochemistry has a significant role in their biological activities. However, the stereoselective synthesis of (*E*)- and (*Z*)-3-alkylidene-2-oxindoles is challenging.[20] Therefore, significant effort has been devoted to the development of an efficient method for the stereoselective synthesis of these (*E*)- or (*Z*)-disubstituted-3-alkylidene-2-oxindoles.

In continuation of our research work toward the synthesis of functionalized 2-oxindoles,[21] we wish to report an efficient protocol for the stereoselective synthesis of 3-alkyliden-2-oxindoles. In our retrosynthetic analysis, the formation of the exocyclic double bond in 3-(diarylmethylene)-2-oxindoles was investigated by a ring-closure procedure of *N*-substituted-2-alkynamides **I** that resulted from the Ugi 4-CR (Ugi 4-component reaction) of benzaldehyde **1**, aniline **2**, phenylpropiolic acid **3**, and isocyanides **4** (Scheme 3).

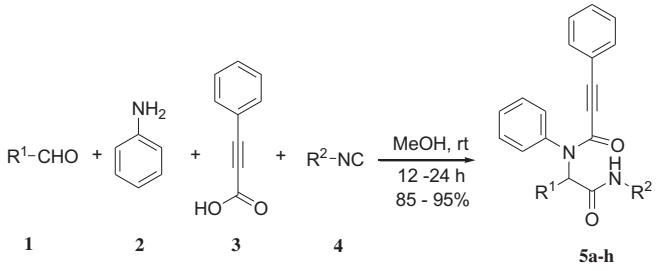


Scheme 3. Retrosynthetic pathway for the synthesis of 3-arylidene-2-oxindoles using Ugi-4MCR.

2. Results and discussions

N-Substituted-2-alkynamides have been widely used as an efficient starting material for the synthesis of 2-oxindole derivatives. Different methodologies have been reported for the synthesis of *N*-substituted-2-alkynamides.[22] The most common approach is the conversion of a carboxylic acid moiety to a more reactive functional group, such as an acyl chloride, and then reaction with amines or acetylides in the presence of a suitable catalyst. They can also be synthesized by other methods, such as: (a) reaction of carboxylic acid containing an alkyne moiety with amines in the presence of coupling reagents, such as DCC;[23] (b) carbonylation of alkynes using CO in the presence of a Pd catalyst and O_2 in high temperature and high pressure;[24] (c) applying an enzymatic reaction;[25] (d) reaction of

isocyanates with Grignard reagent.[26] Drawbacks to these methods are the need for harsh thermal conditions, long reaction times, modest yields, use of expensive reagents, and in some cases multi-step reactions. In this report *N*-substituted-2-alkynamides were synthesized from the reaction of benzaldehyde, aniline, phenylpropiolic acid and isocyanides by an Ugi 4-CR approach (Scheme 4).



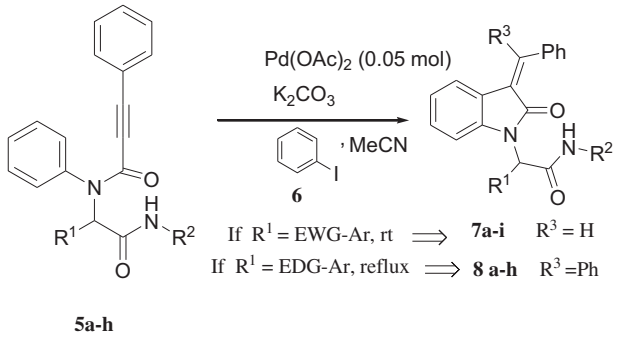
Scheme 4. Synthesis of *N*-substituted-2-alkynamides (**5a**–**h**) via Ugi 4-CR.

Cyclization of *N*-substituted-2-alkylamides was investigated under different conditions in the presence of Brønstead or Lewis acids. Our main focus was on the overall efficiency of this cyclization reaction instead of optimizing factors such as the Lewis acid catalyst type, the catalyst loading, the solvent, and the temperature of reaction media. The results are summarized in Table 1. Reaction of *N*-substituted-2-alkynamide **5a** with iodobenzene was selected as the benchmark reaction. The best results were obtained when $Pd(OAc)_2$ was used as the catalyst in acetonitrile at 60 °C (Scheme 5).

Table 1
Optimization of reaction condition for the synthesis of 3-aryl-2-oxindole (**7a**)

Catalyst loading (mol %)	Temperature	Solvent	Products
CF_3SO_3H (10%)	rt	MeCN	Complex mixture[a]
TFA (10%)	rt and reflux	MeCN	—
SSA[b] (10%)	rt and reflux	MeCN	—
CuI (10%)	rt and reflux	MeCN	—
$AuCl_3$ (20%)	rt and reflux	MeCN	—
$Sc(OTf)_3$ (10%)	rt and reflux	MeCN	—
$Sc(OTf)_3$ (10%)	rt and reflux	[bmim][PF_6]	—
$Pd(OAc)_2$ (5%)	rt	DMF	—
$Pd(OAc)_2$ (5%)	Reflux	DMF	**7** (20%)
$Pd(OAc)_2$ (5%)	rt	MeCN	—
$Pd(OAc)_2$ (5%)	60 °C	MeCN	**7a** (20%), **8a** (80%)

[a] A mixture of different products was obtained and the desired product was only 3%.
[b] SSA (Silica Sulfuric Acid).



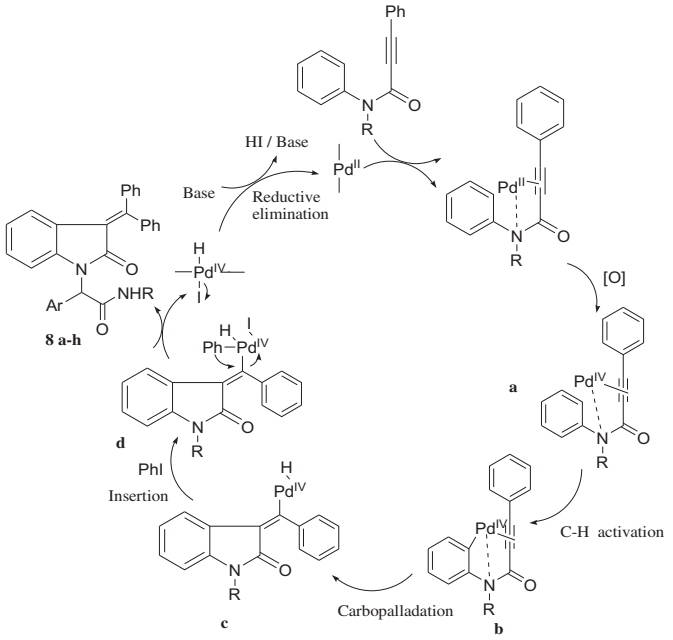
Scheme 5. Pd-catalyzed synthesis of 3-(diarylmethylene) and 3-(arylmethylene)2-oxindoles.

To probe the scope and limitation of this reaction a range of substituted benzaldehydes and isocyanides were examined and finally the cyclization was conducted using catalytic palladium acetate and aryl iodide, which could react via carbopalladation.

Initially, we planned to synthesize the *N*-substituted-2-alkynamides precursors (**5a**–**h**). They could be prepared via Ugi-4CR using the benzaldehyde derivatives, aniline, phenylpropiolic acid, and isocyanides in MeOH at room temperature. Several benzaldehyde derivatives, which contained electron-donating or electron-withdrawing groups were used. With alkyne precursors in hand, we then turned our attention to the preparation of an oxindole scaffold and examined the ability of acetylenic derivatives as efficient substrates for the tandem carbopalladation.

Under the optimized conditions, reaction of *N*-substituted-2-alkynamides, which contained electron-donating groups with iodobenzene (1 equiv), $Pd(OAc)_2$ (5 mol %), potassium carbonate (1 equiv) refluxing in acetonitrile led to the desired diaryl-3-methylidene-2-oxindoles **8a**–**h**. All of the starting materials with electron-donating groups gave the diarylmethyildene-2-oxindoles. But application of the carbopalladation step to substrate (Ph) gave the desired 2-oxindole in 60% yield as mixture of two tetra- and tri-substituted alkenes in a ratio of 80:20, respectively.

According to the known palladium chemistry, the proposed mechanism was shown in Scheme 6 and the reaction procedure could be categorized as follows:



Scheme 6. Proposed mechanism for the synthesis of 3-(diarylmethylene)-2-oxindoles **8a**–**h**.

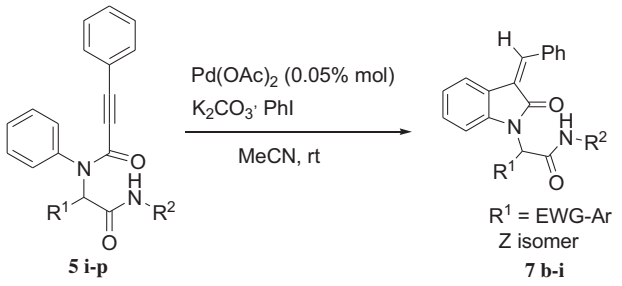
The proposed reaction sequences for the synthesis of 3-(diaryl methylene)-2-oxindoles **8a**–**h** are as follows:

(a) Oxidative-addition of Pd^{II} to Pd^{IV} and complexation of Pd^{IV} with nitrogen and alkyne (structure **a**).
(b) C(sp^3)–H activation (structure **b**).
(c) Insertion of palladium to alkyne moiety and formation of intermediate (Carbopalladation, structure **c**).
(d) Insertion of iodobenzene (structure **d**).
(e) Reductive elimination and finally formation of **8a**–**h**.

The structures of the products were characterized by spectroscopic data (see Experimental section).

To further probe the scope and limitations of this process, we also examined the reaction of benzaldehydes derivatives possessing electron-withdrawing groups. The results were surprising and the (*Z*)-3-arylidene-2-oxindoles were obtained as the sole stereoisomeric product (Scheme 7). This reaction was carried out at room

temperature and the existence of iodobenzene does not affect the reaction process. In this case, the reaction was tested in the presence or absence iodobenzene. In two cases, the product was the same and aryl iodide does not insert in the structure of oxindole. The results are presented in Table 2.



Scheme 7. Pd-catalyzed synthesis of 3-(arylmethylene)2-oxindoles.

The proposed mechanism for the synthesis of *Z*-3-(arylmethylene)-2-oxindoles is shown in Scheme 8 (Table 3).

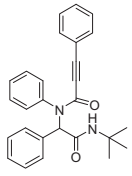
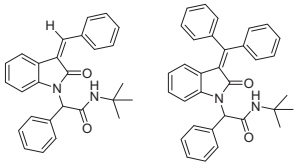
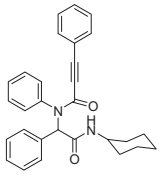
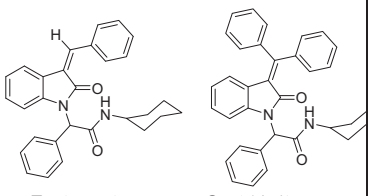
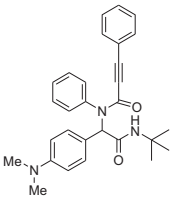
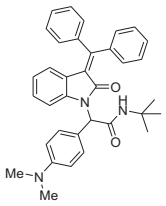
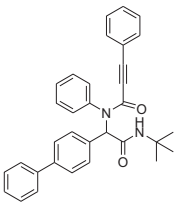
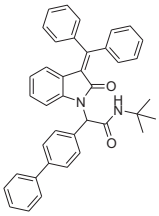
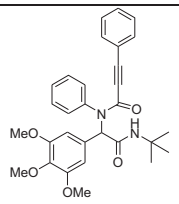
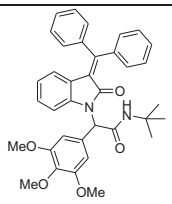
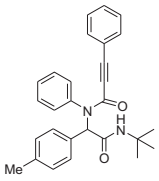
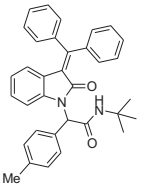
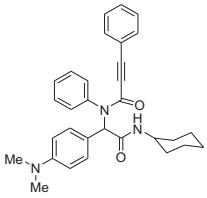
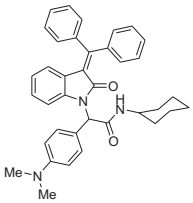
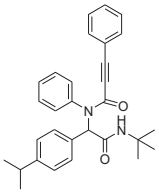
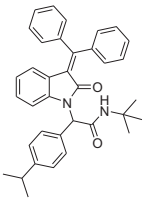
In summary, we have developed an efficient approach to the synthesis of substituted 3-(diarylmethylene)-2-oxindole and *Z*-3-(arylmethylene)-2-oxindole derivatives. The overall reaction involves a sequence of carbopalladation/C–H activation, and C–C bond forming steps and is catalyzed by a palladium catalyst system. The readily accessibility of functionalized starting materials and the generality of this process make it highly valuable in view of the synthetic and medicinal importance of 2-oxindole derivatives.

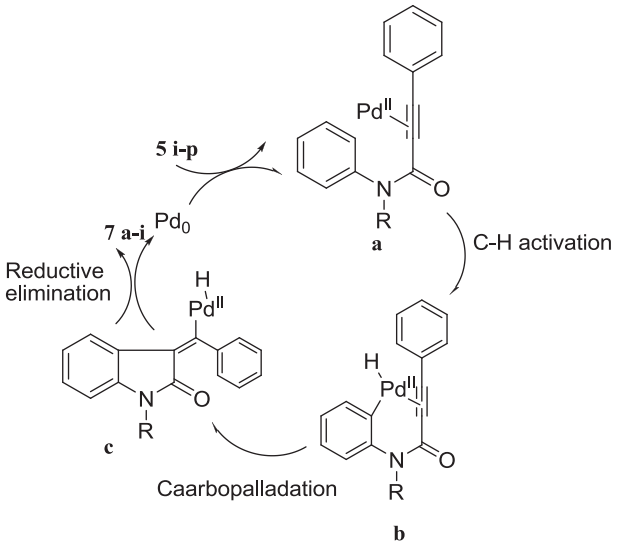
3. Experimental section

3.1. General

Commercially available materials were used without further purification. Melting points were determined on an *Electrothermal*

Table 2
Synthesis of diarylmethylidene-2-oxindoles

N-substituted-2-alkynamide	Products	*N*-substituted-2-alkynamide	Products
 **5a**	 **7a** (4:1) **8a** (60%) / 18h	 **5e**	 **7e** (trace) **8e** (54%) 22h
 **5b**	 **8b** (64%) / 24h	 **5f**	 **8f** (65%) / 17h
 **5c**	 **8c** (54%) / 26h	 **5g**	 **8g** (64%) / 17h
 **5d**	 **8d** (56%) / 26h	 **5h**	 **8h** (63%) / 17h



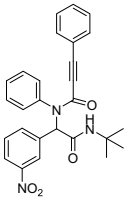
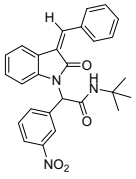
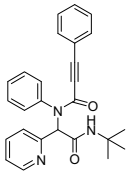
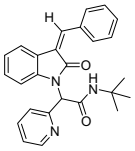
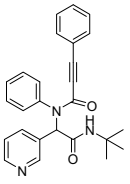
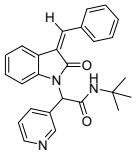
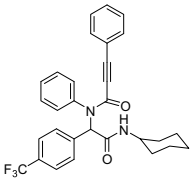
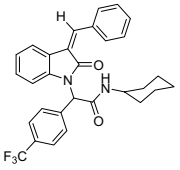
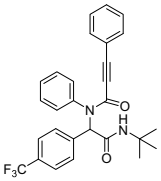
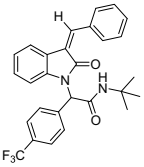
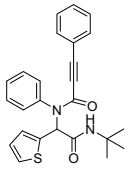
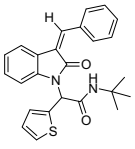
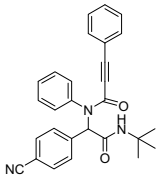
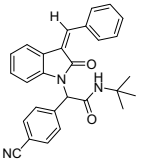
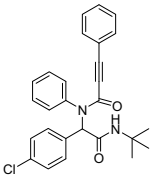
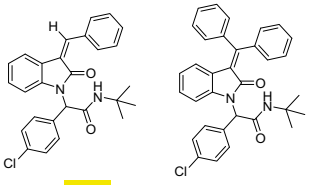
Scheme 8. Proposed mechanism for the synthesis of *Z*-3-(aryl methylene)-2-oxindoles **7a**–**i**.

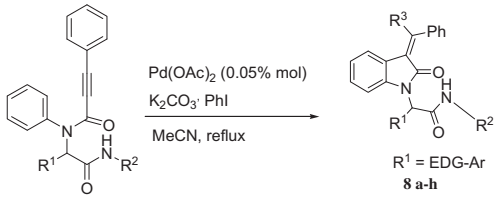
9100 apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR FTLA 2000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on Bruker DRX-500 AVANCE spectrometers at 500 MHz for ^{1}H NMR, and 125 MHz for ^{13}C NMR. $CDCl_3$ was used as solvents. High resolution mass spectra were recorded on HR-MS was recorded on Mass-ESI-POS (Apex Qe-FT-ICR instrument) spectrometer.

3.2. General procedure for the synthesis of *N*-substituted-2-alkynamides: (5a–p)

To a solution of aldehyde **1** (1 mmol) in MeOH (5 mL) was added aniline as a primary amine **2** (1 mmol), and the reaction mixture was stirred at room temperature (25 °C) for 1 h. Then, phenylacetylenecarboxylic acid **3** (1 mmol) was added and stirring was continued for 15 min, followed by addition of isocyanide **4** (1 mmol). The mixture was stirred for 24 h. The progress of the reaction was monitored using TLC (petroleum ether/EtOAc 3:1). After completion of reaction, petroleum ether was added and the solid was filtered and dried.

Table 3
Synthesis of 3-(arylmethylene)-2-oxindoles

Phenylprppiolamide	Products	Phenylprppiolamide	Products
 **5i**	 **7b** (70%) / 12h	 **5m**	 **7f** (68%) / 12h
 **5j**	 **7c** (71%) / 13h	 **5n**	 **7g** (68%) / 14h
 **5k**	 **7d** (80%) / 11h	 **5o**	 **7h** (67%) / 13h
 **5l**	 **7e** (77%) / 12h	 **5p**	 **7i** (1:4) **8i** 60% / 16h



3.3. General procedure for the synthesis of diarylmethylidene-2-oxindoles (8a–h)

The Ugi adduct (**5a**–**h**) (1 mmol) was added to a round bottom flask, which contain acetonitrile (20 mL), $Pd(OAc)_2$ (11 mg, 0.05 equiv), potassium carbonate (414 mg, 3 mmol), and iodobenzene (245 mg, 1.2 mmol). The mixture was heated under reflux for 18–24 h. Reaction progress was monitored using TLC (hexane/EtOAc 3:1). After cooling to room temperature, the reaction mixture was diluted with brine (2×30 mL). The aqueous phase was extracted with EtOAc (2×30 mL). The combined organic phase was separated, dried over sodium sulfate, filtered, and concentrated to dryness in vacuo, and finally purified by column chromatography on silica gel (hexane/ethyl acetate 3:1) to give **8a**–**i** in yields of 54–65%.

*3.3.1. N-tert-Butyl-2-(2-oxo-3-(diphenylmethylene)indolin-1-yl)-2-phenylacetamide (**8a**).* Orange powder (389 mg, 80%); mp: 226–227 °C; R_f (25% EtOAc/hexane) 0.45; ν_{max} (KBr): 1672, 1749, 3316 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.38 (9H, s, *t*-Bu), 5.89 (1H, s, *NH*), 6.15 (1H, s, *CH*), 6.43 (1H, d, *J* 7.0 Hz, H–Ar), 6.63 (1H, t, *J* 8.0 Hz, H–Ar), 6.80 (1H, d, *J* 7.2 Hz, H–Ar), 6.99 (1H, t, *J* 7.0 Hz, H–Ar), 7.26–7.45 (14H, m, H–Ar); δ_C (125 MHz, $CDCl_3$): 28.6, 52.0, 59.0, 112.0, 121.5, 123.0, 123.2, 123.6, 127.8, 128.0, 128.1, 128.5, 128.7, 19.0, 129.2, 129.3, 129.3, 130.2, 134.7, 140.0, 141.3, 141.3, 155.3, 167.1, 167.2; HR-MS (ESI): MH^+ found 487.2380, $C_{33}H_{31}N_2O_2$ requires 487.2380. MNa^+ found 509.2199, $C_{33}H_{30}N_2NaO_2$ requires 509.2200.

*3.3.2. N-tert-Butyl-2-((Z)-3-benzylidene-2-oxoindolin-1-yl)-2-phenylacetamide (**7a**).* White powder (263 mg, 64%); mp: 172–173 °C; R_f (25% EtOAc/hexane) 0.41; ν_{max} (KBr): 1670, 1749, 3343 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.22 (9H, s, *t*-Bu), 6.09 (1H, s, *NH*), 7.04 (1H, t, *J* 7.9 Hz, H–Ar), 7.21–7.37 (11H, m, H–Ar, *CH*, C=*CH*), 7.51 (2H, dd, *J* 8.7, 1 Hz, H–Ar), 7.62 (2H, dd, *J* 8.4, 1 Hz, H–Ar); δ_C (125 MHz, $CDCl_3$): 28.3, 52.0, 76.6, 118.4, 124.5, 126.5, 128.3, 128.7, 128.9, 129.1, 130.2, 130.6, 131.9, 134.9, 136.7, 141.1, 163.1, 166.2; HR-MS (ESI): MH^+ found 411.2067, $C_{27}H_{27}N_2O_2$ requires 411.2067; MNa^+ found 433.1886, $C_{27}H_{26}N_2NaO_2$ requires 433.1887.

*3.3.3. N-tert-Butyl-2-(4-(dimethylamino)phenyl)-2-(2-oxo-3-(diphenylmethylene)indolin-1-yl)acetamide (**8b**).* Orange powder (286 mg, 54%); mp: 272–274 °C; R_f (25% EtOAc/hexane) 0.50; ν_{max} (KBr): 1670, 3318; cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.36 (9H, s, *t*-Bu), 6.07 (1H, s, *NH*), 5.82 (1H, s, *CH*), 6.38 (1H, d, *J* 8.3 Hz, H–Ar), 6.59 (1H, t, *J* 7.7 Hz, H–Ar), 6.67 (2H, d, *J* 7.1 Hz, H–Ar) 6.84 (1H, d, *J* 8.1 Hz, H–Ar), 6.98 (1H, t, *J* 7.8 Hz, H–Ar), 7.27 (2H, d, *J* 7.1 Hz, H–Ar), 7.26–7.45 (10H, m, H–Ar); δ_C (125 MHz, $CDCl_3$): 28.7, 40.3, 51.8, 58.5, 111.7, 112.4, 121.2, 122.0, 122.1, 123.2, 124.0, 127.8, 128.4, 128.9, 129.0, 129.1, 129.3, 130.1, 140.2, 141.5, 141.8, 150.2, 154.5, 167.0, 167.9; HR-MS(ESI) MH^+ found 530.2802, $C_{35}H_{36}N_3O_2$ requires 530.2802; MNa^+ found 552.2621, requires 552.2622.

*3.3.4. N-tert-Butyl-2-(3,4,5-trimethoxyphenyl)-2-(2-oxo-3-(diphenylmethylene)indolin-1-yl)acetamide (**8c**).* Orange powder (323 mg, 56%); mp: 218–220 °C; R_f(25% EtOAc/hexane) 0.52; ν_{max} (KBr): 1673, 1755 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.39 (9H, s, *t*-Bu), 3.79–3.83 (9H, m, OCH_3), 5.92 (1H, s, *NH*), 6.08 (1H, s, *CH*), 6.43 (1H, d, *J* 8.8 Hz, H–Ar), 6.63–6.65 (3H, m, H–Ar), 6.86 (2H, d, *J* 7.9 Hz, H–Ar), 7.01 (1H, t, *J* 7.9 Hz, H–Ar), 7.26–7.45 (10H, m, H–Ar); δ_C (125 MHz, $CDCl_3$): 28.6, 52.0, 56.3, 59.0, 60.8, 105.7, 111.6, 121.6, 123.0, 123.2, 123.5, 127.8, 128.5, 129.0, 129.2, 129.3, 130.1, 130.2, 138.0, 140.0, 141.2, 141.4, 153.4, 155.3, 167.2; HR-MS (ESI) MH^+ found 577.2697, $C_{36}H_{37}N_2O_5$ requires 577.2698; MNa^+ found 599.2518, $C_{36}H_{36}N_2NaO_5$ requires 599.2516; $[M+K]^+$ found 615.2256, $C_{36}H_{36}KN_2O_5$ requires 615.2258.

*3.3.5. N-Cyclohexyl-2-(4-(dimethylamino)phenyl)-2-(2-oxo-3-(diphenylmethylene)indolin-1-yl)acetamide (**8d**).* Orange powder (300 mg, 54%); mp: 204–206 °C; R_f (25% EtOAc/hexane) 0.55; ν_{max} (KBr): 1675, 1742, 3328 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.09–2.00 (10H, m, H–cyclohexyl), 2.92 (6H, s, $N(CH_3)_2$) 3.87 (1H, m, *CH*–cyclohexyl), 5.89 (1H, d, *J* 7.8 Hz, *NH*), 6.14 (1H, s, *CH*), 6.40 (1H, d, *J* 7.7 Hz, H–Ar), 6.60 (1H, t, *J* 7.6 Hz, H–Ar), 6.67 (2H, d, *J* 8.7 Hz, H–Ar), 6.84 (1H, d, *J* 7.9 Hz, H–Ar), 6.99 (1H, t, *J* 7.8 Hz, H–Ar), 7.27 (2H, d, *J* 8.8 Hz, H–Ar), 7.26–7.45 (7H, m, H–Ar); δ_C (125 MHz, $CDCl_3$): 24.8, 25.5, 32.8, 33.0, 40.4, 48.7, 58.0, 111.6, 112.4, 121.3, 121.8, 122.9, 123.3, 123.9, 127.8, 128.4, 128.9, 129.1, 129.2, 129.3, 129.4, 130.2, 140.1, 141.4, 141.7, 150.2, 154.7, 167.0, 167.5; HR-MS (ESI) MH^+ found, 556.2958 $C_{37}H_{38}N_3O_2$ requires 556.2959; MNa^+ found,578.2778 $C_{37}H_{37}N_3NaO_2$ requires 578.2779; MK^+ found 594.2517, $C_{37}H_{37}KN_3O_2$ $[M+K]^+$ requires 594.2518.

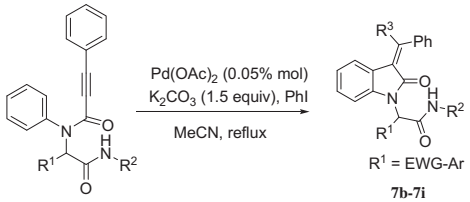
*3.3.6. N-Cyclohexyl-2-(2-oxo-3-(diphenylmethylene)indolin-1-yl)-2-phenylacetamide (**8e**).* Orange powder (333 mg, 65%); mp: 202–204 °C; R_f (25% EtOAc/hexane) 0.40; ν_{max} (KBr): 1655, 1700, 3308 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.11–1.89 (10H, m, H–cyclohexyl), 3.84–3.88 (1H, m, *CH*- cyclohexyl), 5.97 (1H, d, *J* 7.8 Hz, *NH*), 6.20 (1H, s, *CH*), 6.43 (1H, d, *J* 7.5 Hz, H–Ar), 6.63 (1H, td, *J* 7.5, 0.6 Hz, H–Ar), 6.79 (1H, d, *J* 7.9 Hz, H–Ar), 6.98 (1H, td, *J* 7.0, 0.99 Hz, H–Ar), 7.26–7.46 (14H, m, H–Ar); δ_C (125 MHz, $CDCl_3$): 24.7, 25.4, 32.7, 32.8, 48.7, 58.2, 111.6, 121.6, 123.0, 123.2, 123.5, 127.8, 128.0, 128.5, 128.6, 128.9, 129.2, 130.2, 134.4, 140.0, 141.1, 141.2, 155.4, 166.9, 167.1; HR-MS (ESI) MH^+ found 513.2536, $C_{35}H_{33}N_2O_2$ requires 513.2537; MNa^+ found 535.2356, $C_{35}H_{32}N_2NaO_2$ requires 535.2357.

*3.3.7. N-tert-Butyl-2-(biphenyl)-2-(2-oxo-3-(diphenylmethylene)indolin-1-yl)acetamide (**8f**).* Red powder (360 mg, 64%); mp: 173–175 °C; R_f (25% EtOAc/hexane) 0.47; ν_{max} (KBr): 1667, 3317 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.40 (9H, s, *t*-Bu), 5.97 (1H, s, *NH*), 6.20 (1H, s, *CH*), 6.46 (1H, d, *J* 7.7 Hz, H–Ar), 6.63 (1H, t, *J* 7.6 Hz, H–Ar), 6.80 (1H, d, *J* 7.9 Hz, H–Ar), 6.99 (1H, t, *J* 7.5 Hz, H–Ar), 7.26–7.59 (22H, m, H–Ar); δ_C (125 MHz, $CDCl_3$): 28.7, 52.0, 58.5, 111.7, 121.6, 123.0, 123.3, 123.6, 127.1, 127.4, 127.5, 127.9, 128.6, 128.8, 129.3, 129.3, 130.2, 133.7, 140.0, 140.4, 140.9, 141.3, 155.4, 167.2; HR-MS (ESI) MH^+ found 563.2693, $C_{39}H_{35}N_2O_2$ requires 563.2694; MNa^+ found, 585.2512 $C_{39}H_{34}N_2NaO_2$ requires 585.2514.

*3.3.8. N-tert-Butyl-2-(2-oxo-3-(diphenylmethylene)indolin-1-yl)-2-p-tolylacetamide (**8g**).* Orange powder (315 mg, 63%); mp: 259–261 °C; R_f (25% EtOAc/hexane) 0.51; ν_{max} (KBr): 1673, 3414 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.37 (9H, s, *t*-Bu), 2.33 (3H, s, CH_3), 5.87 (1H, s, *NH*), 6.11 (1H, s, *CH*), 6.42 (1H, d, *J* 9.9 Hz, H–Ar), 6.62 (1H, t, *J* 8.2 Hz, H–Ar), 6.81 (1H, d, *J* 8.3 Hz, H–Ar), 6.99 (1H, t, *J* 8.3 Hz, H–Ar), 7.14 (2H, d, *J* 8.0 Hz, H–Ar), 7.28 (2H, d, *J* 8.0 Hz, H–Ar), 7.26–7.45 (10H, m, H–Ar); δ_C (125 MHz, $CDCl_3$): 21.1, 28.6, 51.9, 58.6, 111.7, 121.5, 122.9, 123.2, 123.7, 127.8, 128.1, 128.4, 128.9, 129.1, 129.2, 129.3, 129.4, 130.1, 131.7, 137.8, 140.0, 141.3, 141.4, 155.1, 167.1, 167.3. HR-MS (ESI) MH^+ found 501.2536, $C_{34}H_{33}N_2O_2$ requires 501.2536; MNa^+ found 523.2356, $C_{34}H_{32}N_2NaO_2$ requires 523.2356; MK^+ found 539.2095, $C_{34}H_{32}KN_2O_2$ requires 539.2096.

*3.3.9. N-tert-Butyl-2-(4-isopropylphenyl)-2-(2-oxo-3-(diphenylmethylene)indolin-1-yl)acetamide (**8h**).* Orange powder (105 mg, 20%); mp: 262–264 °C; R_f (25% EtOAc/hexane) 0.50; ν_{max} (KBr): 1675, 3328 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.24 (6H, dd, *J* 6.9, 1.2 Hz, 2× CH_3), 1.38 (9H, s, *t*-Bu), 2.89 (1H, m, $CH(Me)_2$), 5.89 (1H, s, *NH*), 6.14

(1H, s, *CH*), 6.42 (1H, d, *J* 7.7 Hz, H–Ar), 6.63 (1H, t, *J* 7.6 Hz, H–Ar), 6.83 (1H, d, *J* 7.9 Hz, H–Ar), 7.00 (1H, t, *J* 8.1 Hz, H–Ar), 7.20 (2H, d, *J* 8.2 Hz, H–Ar), 7.32 (2H, d, *J* 8.2 Hz, H–Ar), 7.35–7.45 (10H, m, H–Ar); δ_C (125 MHz, $CDCl_3$): 21.8, 23.8, 23.9, 28.6, 33.8, 51.9, 58.7, 111.7, 121.4, 122.9, 123.2, 123.7, 126.8, 127.8, 128.2, 128.4, 128.9, 129.2, 129.2, 129.3, 130.2, 132.0, 140.0, 141.3, 141.5, 148.7, 155.1, 167.1, 167.4; HR-MS (ESI) MH^+ found 529.2849, $C_{36}H_{37}N_2O_2$ requires 529.2850; MNa^+ found 551.2669, $C_{36}H_{36}N_2NaO_2$ requires 551.2669; MK^+ found 567.2408 $C_{36}H_{36}KN_2O_2$ requires 567.2409,.



7b-7i

3.4. General procedure for the synthesis of arylmethylidene-2-oxindoles (7b–i)

The Ugi adduct (**5i**–**p**) (1 mmol) was added to a round bottom flask, which contain acetonitrile (20 mL), $Pd(OAc)_2$ (11 mg, 0.05 equiv), potassium carbonate (414 mg, 3 mmol), and iodobenzene (245 mg, 1.2 mmol). The mixture was heated under reflux condition for 18–24 h. Progress of reaction was monitored by TLC (hexane/EtOAc 3:1). After cooling to room temperature, the reaction mixture was diluted with brine (2×30 mL). The aqueous phase was extracted with EtOAc (2×30 mL). The combined organic phase was separated, dried over sodium sulfate, filtered, and concentrated to dryness in vacuo, and finally purified by column chromatography on silica gel (hexane/ethyl acetate 3:1) to give **7a**–**i** in yields of 60–80%.

*3.4.1. N-tert-Butyl-2-((Z)-3-benzylidene-2-oxoindolin-1-yl)-2-(3-nitrophenyl)acetamide (**7b**).* White powder (91 mg, 20%); mp: 182–184 °C; R_f (25% EtOAc/hexane) 0.47; ν_{max} (KBr): 1673, 1740, 3383 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.29 (9H, s, *t*-Bu), 6.29 (1H, s, *NH*), 7.08 (1H, t, *J*=7.3 Hz, H–Ar), 7.26–7.51 (11H, m, H–Ar, *CH*, C=*CH*), 7.96 (1H, d, *J* 8.0 Hz, H–Ar), 8.15 (1H, d, *J* 8.0 Hz, H–Ar), 8.60 (1H, t, *J* 2.1 Hz, H–Ar); δ_C (125 MHz, $CDCl_3$): 28.3, 52.5, 74.7, 118.0, 123.8, 123.9, 125.1, 128.1, 128.9, 129.4, 129.7, 130.7, 130.8, 131.2, 134.3, 136.0, 136.6, 139.7, 148.3, 162.5, 165.5; HR-MS (ESI) MH^+ found 456.1918, $C_{27}H_{26}N_3O_4$ requires 456.1918; MNa^+ found 478.1737, $C_{27}H_{25}N_3NaO_4$ requires 478.1738.

*3.4.2. N-tert-Butyl-2-((Z)-3-benzylidene-2-oxoindolin-1-yl)-2-(pyridin-3-yl)acetamide (**7c**).* White powder (288 mg, 70%); mp: 161–162 °C; R_f (25% EtOAc/hexane) 0.43; ν_{max} (KBr): 1675, 1744, 3339 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.27 (9H, s, *t*-Bu), 6.25 (1H, s, *NH*), 7.07 (1H, t, *J*=7.4 Hz, H–Ar), 7.21–7.37 (7H, m, H–Ar, *CH*, C=*CH*), 7.44 (2H, d, *J* 6.5 Hz, H–Ar), 7.47 (2H, d, *J* 8.2 Hz, H–Ar), 7.95 (1H, d, *J* 9.3 Hz, H–Ar), 8.53 (1H, d, *J* 4.7 Hz, H–Ar), 8.93 (1H, s, H–Ar); δ_C (125 MHz, $CDCl_3$): 28.3, 52.3, 74.3, 118.1, 123.3, 125.0, 127.8, 128.8, 129.2, 130.4, 130.6, 130.7, 131.3, 136.1, 136.2, 139.6, 149.9, 150.0, 162.6, 165.6; HR-MS (ESI) MH^+ found 412.2019, $C_{26}H_{26}N_3O_2$ requires 412.2019; MNa^+ found, 434.1839 $C_{26}H_{25}N_3NaO_2$ requires 434.1839.

*3.4.3. N-tert-Butyl-2-((Z)-3-benzylidene-2-oxoindolin-1-yl)-2-(4-(trifluoromethyl)phenyl)acetamide (**7d**).* White powder (340 mg, 71%); mp: 182–184 °C; R_f (25% EtOAc/hexane) 0.51; ν_{max} (KBr): 1670, 1751, 3349 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.26 (9H, s, *t*-Bu), 6.21 (1H, s, *NH*), 7.08 (1H, t, *J* 7.3 Hz, H–Ar), 7.25–7.34 (6H, m, H–Ar, *CH*, C=*CH*),7.41 (2H, d, *J* 7.1 Hz, H–Ar), 7.47 (2H, d, *J* 7.9 Hz, H–Ar), 7.59 (2H, d, *J* 8.1 Hz, H–Ar), 7.80 (2H, d, *J* 8.1 Hz, H–Ar); δ_C (125 MHz, $CDCl_3$): 28.3, 52.3, 75.4, 118.1, 122.7, 124.9, 125.7, 127.5, 128.8, 128.9, 129.2, 130.6, 130.7, 130.7, 131.4, 136.2, 138.6, 140.1, 162.7, 165.7; HR-MS (ESI) MH^+ found 479.1941, $C_{28}H_{26}$ $F_3N_2O_2$ 479.1942; MNa^+ $C_{28}H_{25}F_3N_2NaO_2$ found, 501.1760 requires 501.1761.

*3.4.4. N-tert-Butyl-2-((Z)-3-benzylidene-2-oxoindolin-1-yl)-2-(4-cyanophenyl)acetamide (**7e**).* White powder (348 mg, 80%); mp: 182–184 °C; R_f (25% EtOAc/hexane) 0.55; ν_{max} (KBr): 1670, 1751, 3349 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.27 (9H, s, *t*-Bu), 6.21 (1H, s, *NH*), 7.08 (1H, t, *J* 7.9 Hz, H–Ar), 7.25–7.44 (10H, m, H–Ar, *CH*, C=*CH*), 7.60 (2H, d, *J* 8.4 Hz, H–Ar), 7.62 (2H, d, *J* 8.4 Hz, H–Ar); δ_C (125 MHz, $CDCl_3$): 28.3, 52.4, 75.0, 112.9, 118.0, 118.1, 125.1, 127.9, 128.8, 129.3, 130.7, 130.8, 131.2, 132.4, 136.1, 139.8, 162.5, 165.5; HR-MS (ESI) MH^+ found 436.2019, $C_{28}H_{26}N_3O_2$ requires 436.2020; MNa^+ found 458.1839, $C_{28}H_{25}N_3NaO_2$ requires 458.1840.

*3.4.5. N-tert-Butyl-2-((Z)-3-benzylidene-2-oxoindolin-1-yl)-2-(pyridin-2-yl)acetamide (**7f**).* White powder (317 mg, 77%); mp: 159–161 °C; R_f (25% EtOAc/hexane) 0.49; ν_{max} (KBr): 1673, 1755, 3214, 3429 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.34 (9H, s, *t*-Bu), 7.01 (1H, t, *J* 7.7 Hz, H–Ar), 7.14 (1H, s, *NH*), 7.22–7.67 (12H, m, H–Ar, C=*CH*), 8.63 (1H, d, *J* 5.7 Hz, H–Ar), 9.61 (1H, s, *CH*); δ_C (125 MHz, $CDCl_3$): 28.5, 51.8, 117.4, 123.4, 123.5, 125.6, 128.4, 129.0, 129.8, 130.3, 132.2, 137.0, 138.1, 142.1, 147.7, 156.2, 162.7, 165.0; HR-MS (ESI) MH^+ found 412.2019 $C_{26}H_{26}N_3O_2$ requires 412.2019. MNa^+ found 434.1839, $C_{26}H_{25}N_3NaO_2$ requires 434.1839; MK^+ found 450.1578, $C_{26}H_{25}KN_3O_2$ requires 450.1579.

*3.4.6. 2-((Z)-3-Benzylidene-2-oxoindolin-1-yl)-N-cyclohexyl-2-(4-(trifluoromethyl)phenyl)acetamide (**7g**).* White powder (343 mg, 68%); mp: 166–168 °C; R_f (25% EtOAc/hexane) 0.54; ν_{max} (KBr): 1668, 1750, 3342 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.00–1.87 (10H, m, H–cyclohexyl), 3.87–3.92 (1H, m, *CH*–cyclohexyl), 6.31 (1H, d, *J* 7.8, *NH*), 7.01 (1H, t, *J* 7.4 Hz, H–Ar), 7.25–7.46 (10H, m, H–Ar, *CH*, C=*CH*), 7.58 (1H, d, *J* 8.4 Hz, H–Ar), 7.83 (1H, d, *J* 8.4 Hz, H–Ar); δ_C (125 MHz, $CDCl_3$): 24.4, 24.5, 25.2, 32.4, 32.6, 48.9, 75.0, 118.0, 122.6, 124.8, 124.9, 125.7, 125.7, 127.9, 128.7, 128.9, 129.3, 130.7, 130.9, 131.1, 131.2, 136.1, 138.3, 139.7, 162.7, 165.6; HR-MS (ESI) MH^+ found 505.2097, $C_{30}H_{28}F_3N_2O_2$ requires 505.2098; MNa^+ found 527.1917, $C_{30}H_{27}F_3N_2NaO_2$ requires 527.19168; MK^+ found 543.1656, $C_{30}H_{27}F_3KN_2O_2$ requires 543.1657.

*3.4.7. N-tert-Butyl-2-((Z)-3-benzylidene-2-oxoindolin-1-yl)-2-(thiophen-2-yl)acetamide (**7h**).* Yellow powder (283 mg, 68%); mp: 174–176 °C; R_f (25% EtOAc/hexane) 0.43; ν_{max} (KBr): 1670, 1749, 3338 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.24 (9H, s, *t*-Bu), 6.19 (1H, s, *NH*), 6.92 (1H, dd, *J* 4.9, 3.9 Hz, H–thionyl), 7.07 (1H, t, *J* 8.2 Hz, H–Ar), 7.18 (1H, s, *CH*), 7.26–7.52 (9H, m, H–Ar, C=*CH*); δ_C (125 MHz, $CDCl_3$): 28.3, 52.2, 72.3, 117.9, 124.7, 126.6, 126.7, 128.2, 128.7, 128.8, 129.12, 130.4, 130.9, 131.6, 136.2, 136.4, 141.4, 162.6, 166.1; HR-MS (ESI) MH^+ found 417.1631, $C_{25}H_{25}N_2O_2S$; requires 417.1631; MNa^+ found 439.1451, $C_{25}H_{24}N_2NaO_2S$ requires 439.1451.

*3.4.8. N-tert-Butyl-2-((Z)-3-benzylidene-2-oxoindolin-1-yl)-2-(4-chlorophenyl)acetamide (**7i**).* White powder (298 mg, 67%); mp: 184–185 °C; R_f (25% EtOAc/hexane) 0.58; ν_{max} (KBr): 1671, 1747, 3341,3341 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.24 (9H, s, *t*-Bu), 6.15 (1H, s, *NH*), 7.06 (1H, t, *J* 8.5 Hz, H–Ar), 7.23–7.32 (7H, m, H–Ar, *CH*, C=*CH*), 7.41 (2H, d, *J* 7.1 Hz, H–Ar), 7.48 (2H, d, *J* 8.0 Hz, H–Ar), 7.61 (2H, d, *J* 8.5 Hz, H–Ar); δ_C (125 MHz, $CDCl_3$): 28.3, 52.2, 75.6, 118.3, 124.7, 127.1, 128.7, 129.0, 129.1, 129.9, 130.4, 130.7, 131.6, 133.2, 135.0, 136.4, 140.5, 162.8, 165.9; HR-MS (ESI) MH^+ found 445.1677, $C_{27}H_{26}ClN_2O_2$ requires 445.1678; MNa^+ found 467.1497, $C_{27}H$ $_{25}ClN_2NaO_2$ requires 467.1498,.

*3.4.9. N-tert-Butyl-2-(4-chlorophenyl)-2-(2-oxo-3-(diphenylmethylene)indolin-1-yl)acetamide (**8i**).* Orange powder (416 mg, 80%); mp: 250–252 °C; R_f (25% EtOAc/hexane) 0.41; ν_{max} (KBr):

1663, 3311 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.36 (9H, s, *t*-Bu), 5.91 (1H, s, *NH*), 6.09 (1H, s, *CH*), 6.45 (1H, d, *J* 7.8 Hz, H–Ar), 6.66 (1H, t, *J* 8.2 Hz, H–Ar), 6.79 (1H, d, *J* 8.0 Hz, H–Ar), 7.01 (1H, t, *J* 7.9 Hz, H–Ar), 7.26–7.46(13H, m, H–Ar); δ_C (125 MHz, $CDCl_3$): 28.6, 52.0, 58.0, 111.4, 121.8, 123.1, 123.3, 123.3, 127.8, 128.5, 128.8, 129.0, 129.3, 129.4, 129.5, 130.1, 133.1, 134.0, 139.9, 140.8, 141.1, 155.8, 166.7, 167.1; HR-MS (ESI) MH^+ found 521.1988, $C_{33}H_{30}ClN_2O_2$ requires 521.1988; MH^+ found 543.1810, $C_{33}H_{29}ClN_2NaO_2$ requires 543.1810.

Acknowledgements

We gratefully acknowledge the Ministry of Science, Research and Technology of Iran for the financial support. We are also grateful to Prof. R. Gleiter for fruitful and helpful discussions. We express our gratitude to Mr. M. Jalilevand, managing director of Kimia Exir Company for the donation of chemicals/reagents and financial support.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.09.089.

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