

Cite this: *RSC Adv.*, 2018, 8, 34543Received 11th September 2018
Accepted 2nd October 2018

DOI: 10.1039/c8ra07576j

rsc.li/rsc-advances

Advanced palladium free approach to the synthesis of substituted alkene oxindoles *via* aluminum-promoted Knoevenagel reaction†

Daria S. Novikova,^a Tatyana A. Grigoreva,^a Andrey A. Zolotarev,^b Alexander V. Garabadzhiu^a and Vyacheslav G. Tribulovich^a

A synthetic route for the synthesis of C24, as well as for the design of focused libraries of direct AMPK activators was developed based on a convergent strategy. The proposed scheme corresponds to the current trends in C–H bond functionalization. The use of aluminum isopropoxide for the Knoevenagel condensation of oxindole with benzophenones is a noticeable point of this work.

AMP-activated protein kinase (AMPK) has been extensively studied over the last decades. A key role of AMPK in the regulation of energy balance suggests it to be a promising target for energy metabolism-related diseases.¹ To date, AMPK is considered as a therapeutic target in type 2 diabetes, obesity, cardiovascular diseases, atherosclerosis, and cancer.² A number of indirect AMPK activators are already used in clinical practice for their beneficial metabolic effects.³ However, there are no drugs that directly activate AMPK on the pharmaceutical market yet.

The demand for direct AMPK activators inspired pharmaceutical companies to start a campaign to design such molecules.⁴ To date, several classes of compounds that potently activate AMPK have been identified: AICAR and other AMP mimetics,⁵ thienopyridones,⁶ benzimidazoles,⁷ and alkene oxindole derivatives.⁸ The latter activate AMPK by the most interesting and least studied mechanism.⁹ These compounds show good target activity, and C24 (YLF-466D; (*E*)-3-((3-((4-chlorophenyl)(phenyl)methylene)-2-oxindolin-1-yl)methyl) benzoic acid) is the most potent 2-oxindole derivative.⁸ The structure of these compounds provides ample opportunities for both the development of soluble forms and wide structural variations. Small molecules based on 2-oxindole scaffold have a broad spectrum of biological activity.¹⁰ The high druglikeness of these compounds is determined by the fact that 2-oxindole is a tryptophan metabolite and can mimic its affinity to various protein substrates.

Antitumor activity, identified for 3-(benzylidene)indolin-2-ones,¹¹ allows to design multitarget compounds that affect both the metabolic signaling cascades of a cancer cell through AMPK and the proliferative signaling pathway by reactivating p53,¹² since high lipophilicity of the considered structures provides potent binding to the active cavity of the MDM2 protein.¹³

Despite all the advantages of 2-oxindole derivatives in studying the AMPK activation and the small molecule development, the synthetic routes for obtaining this series remain rather laborious. Here, we present a simple and effective route of C24 synthesis. This route takes into account both the possibility of synthesis of small molecule libraries as well as current trends in organic synthesis.

Linear synthesis and convergent synthesis are the main strategies in organic chemistry. The convergent strategy is much more suitable for providing the diversity of a library of complex biologically active compounds. The diversity is realized through divergent stages of the synthetic scheme. However, the divergence of the synthetic scheme at earlier stages leads to the individualization of the synthesis of each compound and, consequently, an increase in the efforts to synthesize a compound library.¹⁴

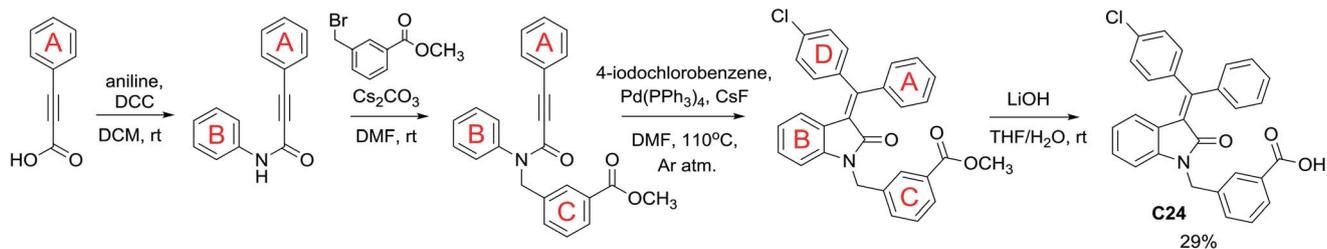
Following the linear scheme, we synthesized C24 from 3-phenylpropionic acid by amidation with aniline, alkylation with 3-(bromomethyl)benzoic acid methyl ester, ring formation of the resulting intermediate, followed by removal of the ester group (Scheme 1).¹⁵ It is interesting that at the ring formation step we observed the formation of dehalogenated compound along with the target product. The resulting mixture of the products cannot be separated by crystallization. Single crystals of mixed composition are formed when crystallizing (Fig. 1). They can be separated only using reversed-phase silica gel, but extremely low solubility of the esters makes the purification process difficult. In addition to the above difficulties, the first stages of the synthesis are divergent, so to introduce

^aLaboratory of Molecular Pharmacology, Saint Petersburg State Institute of Technology (Technical University), Moskovskii pr. 26, Saint Petersburg 190013, Russia. E-mail: dc.novikova@gmail.com

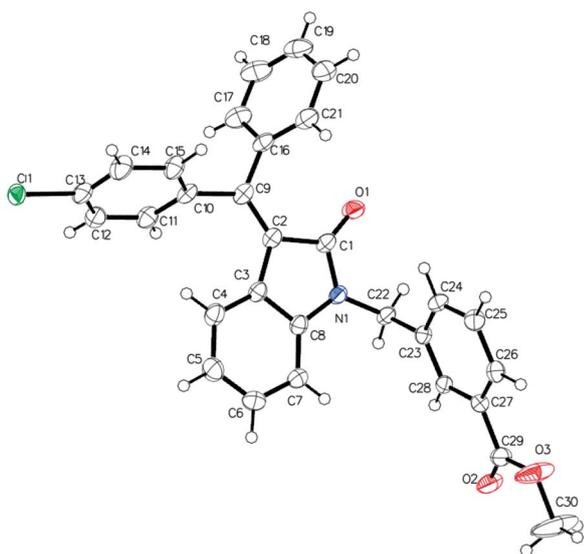
^bDepartment of Crystallography, Saint Petersburg State University, per. Dekabristov 16, Saint Petersburg 199155, Russia

† Electronic supplementary information (ESI) available. CCDC 1585543. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra07576j





Scheme 1 Linear scheme of C24 synthesis.

Fig. 1 ORTEP representation of the crystal structure corresponding to $C_{30}H_{22.25}Cl_{0.75}NO_3$ crystals.

a substituent into ring A it is necessary to obtain substituted phenylpropionic acid, for example, by the Sonogashira coupling. It appears that the diversity is provided before the most difficult stage of building the carbon skeleton.

Current synthetic schemes based on propiolic acid have various modifications, including one pot and domino multi-component ones.¹⁶ However, the modern names do not relieve them of the shortcomings inherent to the linear scheme; moreover, the use of active catalysts can lead to undesirable rearrangements of the carbon skeleton of the target substrate.¹⁷

The convergent synthesis (Scheme 2) can be implemented based on the route obtained using obvious disconnections. The

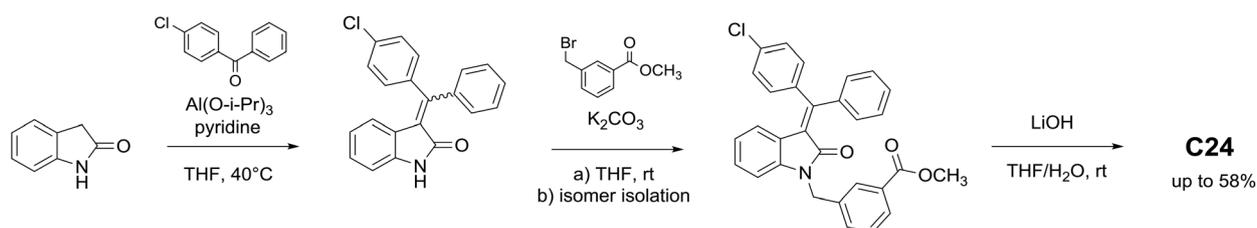
simplest way to build the carbon skeleton of substituted alkene oxindoles is to perform the Knoevenagel condensation of oxindole with benzophenones. The condensation of oxindole with aldehydes and alkylphenones proceeds practically with quantitative yields under common conditions: toluene, pyrrolidine, azeotropic distillation of water. Reduction of yields is observed only in the case of ketones and aldehydes substituted in position 2 of the aromatic ring. However, there is the difficulty to realize the condensation of oxindole with benzophenones,¹⁸ and under the same conditions the reaction product is formed only in trace amounts when benzophenone is taken as a carbonyl compound (Table 1).

Varying of solvents and bases does not lead to a significant increase in the conversion of the starting compounds. A positive result was reached using equimolar amounts of anhydrous ammonium acetate; the degree of oxindole conversion was increased, and the condensation product was obtained in 20% yield (Table 2).

Among the modern methods for performing the Knoevenagel condensation, we should highlight a method with intermediate formation of titanium enolate,¹⁹ which was successfully used for the synthesis of 3-alkylidene oxindoles.²⁰ We found that the proposed method shows good results not only for benzophenone condensation, as it was shown, but also when using diversely substituted benzophenones, for example 4-chlorobenzophenone (Table 2).

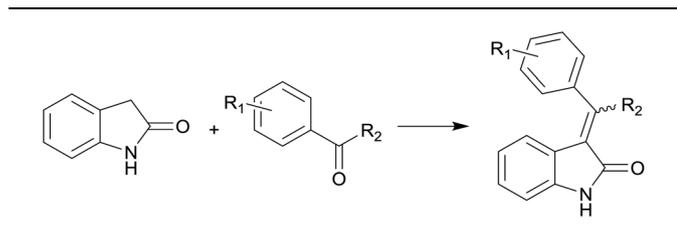
However, the reaction turned out to be very sensitive to the quality of titanium isopropoxide used. Long-term storage of the reagent resulted in a significant drop in the yield of the target compound. Accordingly, high requirements are imposed on the THF dryness (distillation over LAH).

When looking for less capricious, but no less effective condensation catalyst, we paid attention to aluminum isopropoxide. The homogeneous catalysis of the Knoevenagel



Scheme 2 Convergent scheme of C24 synthesis.



Table 1 Knoevenagel condensation of carbonyl compounds with unsubstituted oxindole

Entry	R ₁	R ₂	Time, h	Yield (<i>E/Z</i> ratio)
1	4-Cl	H	0.25	96 (63/36)
2	2-Cl	H	3	72 (98/2)
3	H	CH ₃	0.5	94 (96/4)
4	4-Cl	CH ₃	1	91 (96/4)
5	2-Cl	CH ₃	3	65 (99/1)
6	H	C ₂ H ₅	2	85 (95/5)
7	H	<i>n</i> -C ₃ H ₇	2	76 (95/5)
8	3',4'-Methylenedioxy	CH ₃	1	80 (98/2)
9	H	Ph	24	Traces
10	4-Cl	Ph	24	Traces ^b
11	4-OCH ₃	Ph	24	Traces ^b

^a Reaction conditions: 2-oxindole (1 equiv.), corresponding ketone (1.2 equiv.), pyrrolidine (2 equiv.), toluene, reflux with the Dean-Stark trap. ^b *E/Z* ratio not determined.

reaction by aluminum alkoxides has not been described previously, although studies on heterogeneous catalysis using aluminum oxide were conducted.²¹

We proposed that aluminum isopropoxide is able of similar formation of enolates with carbonyl groups of oxindole observed for titanium isopropoxide. Thus, first using aluminum isopropoxide as a condensing agent in the Knoevenagel type

reaction, we obtained a series of condensed oxindole derivatives with good yields under mild conditions (Table 3). Aluminum isopropoxide can be readily obtained in the laboratory, and its prolonged storage does not lead to a significant drop in the reaction yields.

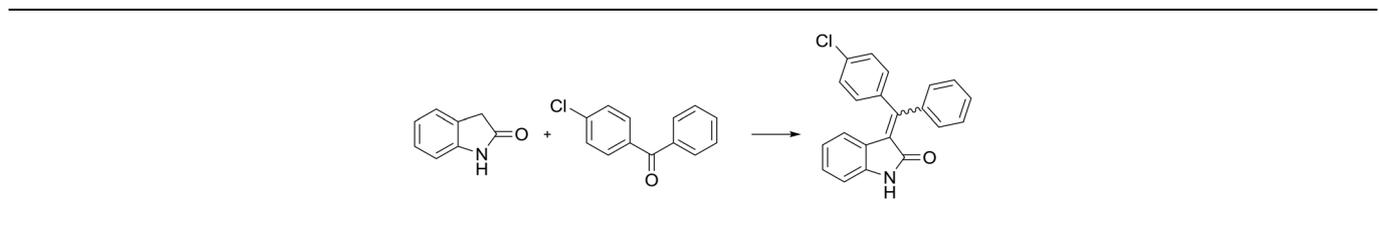
It should be noted that due to the presence of the double bond in position 3, alkene oxindoles exist as *E*- and *Z*-isomers exhibiting different biological activity.¹⁵ This requires the isolation of single isomers and separate biological evaluation.

In the case of the condensation of aldehydes and alkylphenones in the presence of pyrrolidine, *E*-isomers are predominantly formed. However, it was shown that the condensation of oxindole with acetophenone and propiophenone *via* titanium enolates leads to a prevalence of *Z*-isomer in the product mixture.²⁰

Titanium- and aluminum-promoted condensation of oxindole with 4-chlorobenzophenone resulted in similar ratio of *E*- and *Z*-isomers when compared (*E/Z* ratio 40/60 and 37/63, respectively). This *E,Z*-isomer mixture of the condensation products can be successfully separated by column chromatography ($R_f(E) = 0.32$, $R_f(Z) = 0.46$, *n*-hexane/ethyl acetate 3 : 1). The isomers can be clearly distinguished in ¹H NMR spectra by the chemical shifts of protons H₄ and H₅ of the oxindole core (Fig. 2).

Despite the differences in the *E,Z*-isomer ratio obtained during the condensation of oxindoles with aldehydes or unsymmetrical ketones under different synthetic conditions, from the preparative point of view, optimization of the selectivity of this stage by manipulation with the reaction mechanism is meaningless due to a relatively easy transition between the *E,Z*-isomers.

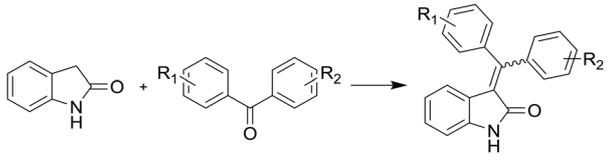
One isomer can be transferred to another by UV irradiation until the equilibrium is reached.²² The isomerization reaction

Table 2 Knoevenagel reaction conditions

Entry	Base/catalyst	Amount	Solvent	Yield
1	Piperidine	2	Ethanol	Trace
2	NH ₃	Excess ^a	Toluene	Trace
3	NaH	1.1	THF	8
4	NaH	1.1	DMF	6
5	NaOH	1	Ethanol	5
6	NaOH	1	Butanol	7
7	NH ₄ COOCH ₃	Excess ^a	Toluene	20
8	Pyridine/Ti[OCH(CH ₃) ₂] ₄	3/2	THF (rt)	58
9	Pyridine/Ti[OCH(CH ₃) ₂] ₄	3/2	THF (60 °C)	86
10	Pyridine/Ti[OCH(CH ₃) ₂] ₄ , (2 days of storage)	3/2	THF (60 °C)	34
11	Pyridine/Ti[OCH(CH ₃) ₂] ₄ , (5 days of storage)	3/2	THF (60 °C)	Trace

^a About 20 equivalents.



Table 3 Aluminum-promoted Knoevenagel condensation^a


Entry	R ₁	R ₂	Yield ^b	Isomer ratio, <i>E/Z</i> ^c
1	H	H	76	—
2	2-Cl	H	80	62/38
3	4-Cl	H	82	37/63
4	4-Cl	4-Cl	86	—
5	4-Cl	2,4-Cl	83	56/44
6	4-OH	H	77	50/50
7	4-OCH ₃	H	73	38/62
8	3-CH ₃	4-Cl	83	42/58
9	3-CH ₃	4-OH	80	50/50
10	4-CH ₃	4-Cl	79	46/54
11	4-CH ₃	4-OH	72	50/50

^a Reaction conditions: 2-oxindole (1 equiv.), benzophenone (1.2 equiv.), pyridine (2 equiv.), aluminum isopropoxide (3 equiv.), THF, 40 °C, 12 h.

^b Total yield is given (for both *E*- and *Z*-isomer). ^c Determined by NMR after work up.

proceeds without the by-product formation. Particularly, the *Z/E* equilibrium ratio for the condensation products of oxindole with 4-chlorobenzophenone is 51/49. Using a series of sequential irradiations and separations, it is possible to achieve the preparative yield of the desired isomer (*E*- or *Z*-isomer) up to 80%.

Thus, the most rational way to obtain individual isomeric forms of the compounds is to separate the mixture at the final stages of the synthetic scheme. So, methyl ester of C24 can be prepared by direct alkylation of the *E,Z*-isomer mixture of the condensation products with 3-(bromomethyl)benzoic acid methyl ester as an alkylating agent (Table 4) and subsequent separation of the alkylated derivatives ($R_f(E_{\text{alk}}) = 0.21$, $R_f(Z_{\text{alk}}) = 0.30$, *n*-hexane/ethyl acetate 6 : 1).

Alkaline hydrolysis in a water–THF mixture is the final stage of the synthesis. It is carried out using the trivial procedure with yields close to quantitative. Scheme 2 represents a simple and effective route based on the convergent strategy, which can be used for obtaining C24 with the total yield of 58%, as well as for the synthesis of 3-(benzylidene)indolin-2-one series.

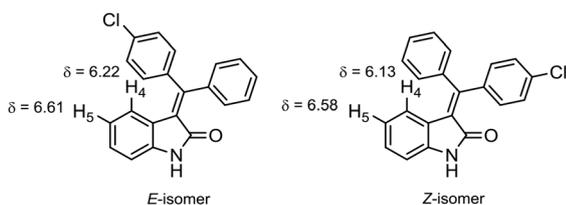
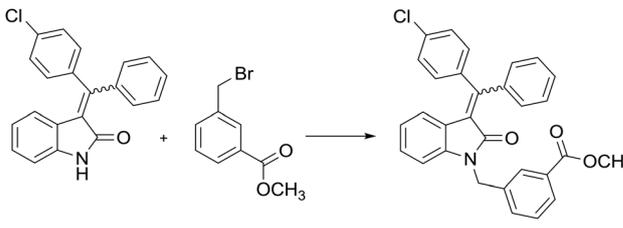


Fig. 2 Chemical shifts of characteristic proton signals for pair of 3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one isomers.

Table 4 Alkylation of 3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one with 3-(bromomethyl)benzoic acid methyl ester



Entry	Base	Amount	Solvent	Yield
1	Na ₂ CO ₃	3	DMF	4
2	K ₂ CO ₃	3	DMF	93
3	NaH	1.5	THF	62
4	NaH	1.1	DMF	78–83 ^a
5	TEA	3	DMF	Trace
6	TEA	3	Toluene	29
7	K ₂ CO ₃	3	DMSO	47
8	K ₂ CO ₃	3	Acetone	34

^a Simultaneous hydrolysis of ester group was observed.

Conclusions

In summary, we developed advanced route of C24 synthesis within the convergent strategy. The used synthetic methods, despite of their simplicity, correspond to the current trends in the C–H bond functionalization without recruiting halogens or halogenoids as leaving groups.²³ Thus, using the previously proposed schemes the halogen acts as a leaving group three times during the synthesis,^{15,16} while in the developed scheme only once at the *N*-alkylation step. One of the most interesting points of the work is the use of aluminum isopropoxide as a condensing agent in the Knoevenagel reaction. The given scheme and methods of synthesis provide the most comfortable opportunity for the development of focused libraries with high variability of external fragments including those with hydroxy group.

Experimental

All starting compounds and reagents used, except 2-oxindole which was obtained according to the known procedure,²⁴ are commercially available.

The progress of reactions was monitored by TLC on Silica gel 60 F254 plates (Merk) using *n*-hexane/ethyl acetate eluent. Purification of the products was carried out using an Isolera Four flash chromatograph on SNAP KP-Sil 100 g cartridges (Biotage) with *n*-hexane/ethyl acetate eluent. For separation of the mixture of C24 methyl ester and its dehalogenated product, an Omnifit glass column (DIBA) packed with LiChroprep RP-18 sorbent 25–40 μm (Merck) was used.

¹H and ¹³C NMR spectra were recorded on a Bruker Avance III 400 (400 MHz) device in DMSO-*d*₆. To determine the spatial configuration of the compounds (*E* or *Z* isomer), previously obtained crystallographic data or NOESY/ROESY spectra were considered. The isomer ratio was evaluated only by ¹H-NMR, since



the isomers have different absorption at 254 nm commonly used for detection in chromatographic devices. Mass spectra were recorded on a LCMS-2020 device (Shimadzu) with a single quadrupole detector under positive mode, electrospray ionization (ESI).

General procedure for C24 synthesis using the linear scheme

Originally, the synthesis of C24 was carried out according to the known procedure¹⁵ with some modifications concerning mainly the work up of the reactions and the use of preobtained tetrakis(triphenylphosphine)palladium instead of *in situ* generation (total yield 29%).

***N*,3-Diphenylpropiolamide.** Aniline (3 g, 0.032 mol) and phenylpropionic acid (5.12 g, 0.035 mol) were dissolved in 100 mL dichloromethane, and then 7.7 g *N,N*-dicyclohexylcarbodiimide (0.037 mol) was added in one portion at 0 °C. The reaction mixture was intensively stirred overnight at room temperature. The mixture then was poured into water and extracted with dichloromethane (3 × 50 mL). The organic layers were combined, dried over anhydrous Na₂SO₄, the solvent was then evaporated under reduced pressure. The product was purified by flash chromatography (*n*-hexane/ethyl acetate 9 : 1). Colorless crystals in 78% yield (5.44 g), mp 125–126 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 10.84 (s, 1H), 7.66 (d, *J* = 7.7, 4H), 7.55–7.47 (m, 3H), 7.34 (t, *J* = 7.8, 2H), 7.11 (t, *J* = 7.3, 1H); MS (ESI) *m/z*: 222 [M + H]⁺.

Methyl 3-((*N*,3-diphenylpropiolamido)methyl)benzoate. *N*,3-Diphenylpropiolamide (4 g, 0.018 mol), methyl 3-(bromomethyl)benzoate (4.8 g, 0.022 mol) and cesium carbonate (8.8 g, 0.027 mol) were dissolved in 100 mL dimethylformamide and stirred overnight at room temperature. The solvent was evaporated under reduced pressure, and then 200 mL water was added to the residue. The precipitate was filtered off, dissolved in ethyl acetate, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by recrystallization from isopropanol to give 5.8 g (87%). Colorless crystals, mp 110–111 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.89–7.83 (m, 2H), 7.54–7.30 (m, 10H), 5.08 (s, 2H), 3.85 (s, 3H); MS (ESI) *m/z*: 370 [M + H]⁺.

(*E*)-3-((3-((4-Chlorophenyl)(phenyl)methylene)-2-oxindolin-1-yl)methyl)benzoic acid methyl ester. Tetrakis(triphenylphosphine)palladium (0.58 g, 0.0005 mol), 1-chloro-4-iodobenzene (2.6 g, 0.011 mol) and cesium fluoride (4.6 g, 0.03 mol) were added to a solution of methyl 3-((*N*,3-diphenylpropiolamido)methyl)benzoate (3.7 g, 0.01 mol) in 50 mL dimethylformamide. The reaction mixture was stirred for 3 h at 110 °C under argon atmosphere, and then 200 mL water was added. The mixture was extracted with ethyl acetate, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The mixture of products was first isolated by flash chromatography using *n*-hexane/ethyl acetate eluent (9 : 1), and then the title product was separated from dehalogenated product on a reversed-phase silica gel column with methanol/water eluent (3 : 1). Yellow crystals in 49% yield; mp 181–182 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.96 (s, 1H), 7.87 (d, *J* = 7.7, 1H), 7.57 (d, *J* = 7.8, 1H), 7.54 (d, *J* = 8.4, 2H), 7.47 (t, *J* = 7.7, 1H), 7.39–7.29 (m, 7H), 7.12 (t, *J* = 7.6, 1H), 6.87 (d, *J* = 7.8, 1H), 6.69

(t, *J* = 7.7, 1H), 6.33 (d, *J* = 7.6, 1H), 4.96 (s, 2H), 3.87 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ (ppm): 166.48, 166.06, 153.00, 142.50, 140.26, 139.90, 137.98, 134.52, 132.59, 131.17, 130.46, 130.36, 129.80, 129.71, 129.63, 129.38, 128.65, 128.45, 128.23, 124.29, 122.97, 122.85, 122.00, 109.41, 52.66, 42.62; MS (ESI) *m/z*: 480 [M + H]⁺.

(*E*)-3-((3-((4-Chlorophenyl)(phenyl)methylene)-2-oxindolin-1-yl)methyl)benzoic acid (C24). Lithium hydroxide (1.2 g, 0.05 mol) dissolved in 50 mL water was added to the corresponding methyl ester (2.4 g, 0.005 mol) dissolved in 50 mL THF. The reaction mixture was stirred at rt and monitored by TLC. The organic solvent was then distilled off. The mixture was acidified with 15% HCl, the precipitate was filtered off, washed with 50 mL water and dried. The crude product was purified by recrystallization from ethyl acetate. Yellow crystals in 88% yield; mp 204–206 °C (decomp.); ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.91 (s, 1H), 7.85 (d, *J* = 7.7, 1H), 7.61–7.53 (m, 3H), 7.47 (t, *J* = 7.7, 1H), 7.41–7.30 (m, 7H), 7.15 (t, *J* = 7.8, 1H), 6.92 (d, *J* = 7.8, 1H), 6.73 (t, *J* = 7.5, 1H), 6.29 (d, *J* = 7.7, 1H), 4.97 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ (ppm): 167.55, 166.04, 152.98, 142.55, 140.27, 139.91, 137.75, 134.48, 132.22, 131.59, 131.16, 130.32, 129.81, 129.73, 129.44, 129.36, 128.79, 128.53, 128.24, 124.29, 122.96, 122.81, 122.00, 109.43, 42.66; MS (ESI) *m/z*: 466 [M + H]⁺.

General procedure for Knoevenagel condensation of carbonyl compounds (aldehydes or alkylphenones) with oxindol

2-Oxindole (2 g, 0.015 mol) was suspended in 50 mL of toluene. The corresponding ketone (0.018 mol, 1.2 equiv.), 2.5 mL of pyrrolidine (0.03 mol, 2 equiv.) were added to the suspension. The reaction mixture was refluxed with the Dean–Stark trap. The reaction was monitored by TLC until the starting oxindole disappeared. Then the mixture was cooled, the solvent was evaporated under reduced pressure. The crude product was treated with a small amount of ethyl acetate and then filtered off, or recrystallized from *n*-hexane/ethyl acetate, or purified by flash chromatography using *n*-hexane/ethyl acetate eluent (if pair of isomers formed).

3-(4-Chlorobenzylidene)indolin-2-one. Yellow crystals in 96% total yield. *E*-isomer: ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 10.63 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.60 (s, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.7, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ (ppm): 168.93, 143.55, 134.75, 134.59, 133.83, 131.59, 130.85, 129.33, 128.67, 122.95, 121.69, 121.12, 110.68; MS (ESI) *m/z*: 256 [M + H]⁺. *Z*-isomer: ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 10.67 (s, 1H), 8.40 (d, *J* = 8.6 Hz, 2H), 7.79 (s, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.28–7.15 (m, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ (ppm): 167.55, 141.38, 135.55, 135.29, 134.01, 133.31, 129.69, 128.69, 127.86, 125.16, 121.59, 120.42, 109.90; MS (ESI) *m/z*: 256 [M + H]⁺.

(*E*)-3-(2-Chlorobenzylidene)indolin-2-one. Yellow crystals in 72% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 10.67 (s, 1H), 7.77 (dd, *J* = 7.0, 2.2 Hz, 1H), 7.64 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.55–7.47 (m, 2H), 7.59 (s, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* =



7.6 Hz, 1H), 6.88 (d, $J = 7.7$ Hz, 1H), 6.81 (t, $J = 7.6$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 168.55, 143.63, 133.41, 133.36, 131.94, 131.73, 131.12, 130.79, 130.30, 130.01, 127.90, 123.04, 121.75, 120.98, 110.75; MS (ESI) m/z : 256 [M + H] $^+$.

(E)-3-(1-Phenylethylidene)indolin-2-one. Yellow crystals in 94% yield; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.49 (s, 1H), 7.54–7.43 (m, 3H), 7.30 (d, $J = 6.9$, 2H), 7.01 (t, $J = 7.6$, 1H), 6.76 (d, $J = 7.7$, 1H), 6.50 (t, $J = 7.6$, 1H), 5.98 (d, $J = 7.7$, 1H), 2.71 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 169.30, 154.15, 143.08, 141.20, 129.67, 128.83, 128.73, 126.74, 123.99, 123.17, 122.71, 120.85, 109.72, 22.49; MS (ESI) m/z : 236 [M + H] $^+$.

(E)-3-(1-(4-Chlorophenyl)ethylidene)indolin-2-one. Yellow crystals in 91% yield; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.51 (s, 1H), 7.54 (d, $J = 8.3$, 2H), 7.35 (d, $J = 8.3$, 2H), 7.04 (t, $J = 7.6$, 1H), 6.77 (d, $J = 7.7$, 1H), 6.57 (t, $J = 7.6$, 1H), 6.07 (d, $J = 7.7$, 1H), 2.68 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 169.16, 152.49, 141.75, 141.32, 133.56, 129.75, 128.98, 128.94, 124.33, 122.92, 122.66, 120.99, 109.84, 22.29; MS (ESI) m/z : 270 [M + H] $^+$.

(E)-3-(1-(2-Chlorophenyl)ethylidene)indolin-2-one. Yellow crystals in 65% yield; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.48 (s, 1H), 7.32–7.25 (m, 2H), 7.49 (dd, $J = 6.9$, 2.4 Hz, 1H), 7.41 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.05 (t, $J = 7.7$, 1H), 6.79 (d, $J = 7.6$, 1H), 6.59 (t, $J = 7.7$, 1H), 6.04 (d, $J = 7.8$, 1H), 2.65 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 168.67, 151.97, 142.14, 141.68, 135.22, 134.43, 129.64, 129.19, 128.09, 127.27, 126.67, 123.75, 123.32, 121.23, 110.26, 22.18; MS (ESI) m/z : 270 [M + H] $^+$.

(E)-3-(1-Phenylpropylidene)indolin-2-one. Yellow crystals in 85% yield; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.52 (s, 1H), 7.56–7.45 (m, 3H), 7.27 (d, $J = 6.7$, 2H), 7.03 (t, $J = 7.5$, 1H), 6.76 (d, $J = 7.7$, 1H), 6.50 (t, $J = 7.5$, 1H), 5.85 (d, $J = 7.7$, 1H), 3.24 (q, $J = 7.4$, 2H), 1.00 (t, $J = 7.7$, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 168.94, 159.65, 141.36, 141.32, 129.61, 128.78, 127.18, 123.60, 123.23, 122.80, 120.85, 109.70, 27.37, 12.26; MS (ESI) m/z : 250 [M + H] $^+$.

(E)-3-(1-Phenylbutylidene)indolin-2-one. Yellow crystals in 76% yield; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.55 (s, 1H), 7.55–7.45 (m, 3H), 7.27 (d, $J = 7.9$ Hz, 2H), 7.03 (t, $J = 7.6$ Hz, 1H), 6.76 (d, $J = 7.6$ Hz, 1H), 6.51 (t, $J = 7.7$ Hz, 1H), 5.85 (d, $J = 7.7$ Hz, 1H), 3.23 (t, $J = 7.6$ Hz, 2H), 1.44–1.34 (m, 2H), 0.90 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 169.04, 158.26, 141.50, 141.30, 129.61, 128.78, 127.13, 124.25, 123.22, 122.80, 120.84, 109.67, 35.77, 20.85, 14.21; MS (ESI) m/z : 264 [M + H] $^+$.

(E)-3-(1-(Benzo[*d*][1,3]dioxol-5-yl)ethylidene)indolin-2-one. Yellow crystals in 80% yield; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.56 (s, 1H), 7.09–7.01 (m, 2H), 6.95 (d, $J = 1.3$ Hz, 1H), 6.81 (dd, $J = 7.9$, 1.5 Hz, 1H), 6.78 (d, $J = 7.7$, 1H), 6.63 (t, $J = 7.7$, 1H), 6.25 (d, $J = 7.7$, 1H), 6.11 (s, 2H), 2.66 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 169.33, 154.01, 148.37, 147.76, 141.10, 136.65, 128.67, 124.06, 123.23, 122.82, 120.96, 120.61, 109.70, 109.45, 107.65, 101.80, 22.57; MS (ESI) m/z : 280 [M + H] $^+$.

Procedure for aluminum isopropoxide preparation

Finely flattened aluminium (2.7 g, 0.1 mol) in 100 mL isopropanol with a catalytic amount of iodine was refluxed with

drying tube until aluminum was completely dissolved. The isopropanol was distilled off and the crude product was immediately purified by distillation (0.4 bar, 134–137 °C). Freshly distilled aluminum isopropoxide was obtained as high-viscosity liquid in 94% yield, solidifying within several hours.

General procedure for aluminum-promoted Knoevenagel condensation of benzophenones

2-Oxindole (2 g, 0.015 mol) was dissolved in dried and freshly distilled THF, the corresponding benzophenone (0.018 mol), pyridine (2.42 mL, 0.03 mol) and aluminum isopropoxide (9.2 g, 0.045 mol) were added. The reaction mixture was heated to 40 °C and kept overnight. Then the reaction mixture was quenched with 3% Na₂CO₃ solution, extracted with ethyl acetate, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The product (mixture of products) was isolated by flash chromatography with *n*-hexane/ethyl acetate eluent.

3-(Diphenylmethylene)indolin-2-one. Yellow crystals in 76% yield; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.49 (s, 1H), 7.50–7.47 (m, 3H), 7.35–7.25 (m, 7H), 7.09 (td, $J = 7.7$, 0.8 Hz, 1H), 6.78 (d, $J = 7.7$ Hz, 1H), 6.57 (t, $J = 7.6$ Hz, 1H), 6.09 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.57, 153.20, 142.46, 141.81, 140.30, 130.14, 129.65, 129.47, 129.43, 128.93, 128.89, 128.09, 125.28, 123.75, 123.12, 120.92, 109.88; MS (ESI) m/z : 298 [M + H] $^+$.

3-((2-Chlorophenyl)(phenyl)methylene)indolin-2-one. Yellow crystals in 80% total yield. *E*-isomer: ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.49 (s, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.36–7.30 (m, 5H), 7.29–7.25 (m, 2H), 7.12 (t, $J = 7.7$ Hz, 1H), 6.79 (d, $J = 7.7$ Hz, 1H), 6.65 (t, $J = 7.7$ Hz, 1H), 6.20 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.41, 151.55, 142.57, 140.53, 140.03, 134.22, 131.09, 130.22, 129.77, 129.71, 129.07, 128.17, 125.63, 123.47, 123.06, 121.10, 110.01; MS (ESI) m/z : 332 [M + H] $^+$. *Z*-isomer: ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.52 (s, 1H), 7.52–7.47 (m, 3H), 7.41–7.36 (m, 2H), 7.33–7.27 (m, 4H), 7.10 (t, $J = 7.6$ Hz, 1H), 6.78 (d, $J = 7.8$ Hz, 1H), 6.59 (t, $J = 7.6$ Hz, 1H), 6.11 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.55, 151.43, 142.56, 141.30, 139.11, 133.70, 132.00, 129.73, 129.61, 128.95, 128.19, 128.08, 125.79, 123.52, 123.18, 121.01, 109.98; MS (ESI) m/z : 332 [M + H] $^+$.

3-((4-Chlorophenyl)(phenyl)methylene)indolin-2-one. Yellow crystals in 82% total yield. *E*-isomer: mp 153–155 °C (decomp.); ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.46 (s, 1H), 7.54 (d, $J = 8.3$ Hz, 2H), 7.29–7.36 (m, 5H), 7.24–7.28 (m, 2H), 7.10 (t, $J = 7.6$ Hz, 1H), 6.78 (d, $J = 7.7$ Hz, 1H), 6.63 (t, $J = 7.6$ Hz, 1H), 6.22 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.41, 151.55, 142.57, 140.52, 140.03, 134.21, 131.07, 130.19, 129.76, 129.71, 129.06, 128.16, 125.63, 123.47, 123.06, 121.09, 110.00; MS (ESI) m/z : 332 [M + H] $^+$. *Z*-isomer: mp 229–230 °C; ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.52 (s, 1H), 7.46–7.51 (m, 3H), 7.38 (d, $J = 8.5$ Hz, 2H), 7.27–7.33 (m, 4H), 7.09 (t, $J = 7.6$ Hz, 1H), 6.79 (d, $J = 7.7$ Hz, 1H), 6.58 (t, $J = 7.6$ Hz, 1H), 6.13 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.56, 151.41, 142.57, 141.29, 139.11, 133.71, 131.98, 129.71,



129.59, 128.94, 128.18, 125.81, 123.53, 123.19, 121.00, 109.98; MS (ESI) m/z : 332 $[M + H]^+$.

3-(Bis(4-chlorophenyl)methylene)indolin-2-one. Yellow crystals in 86% yield; 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.54 (s, 1H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.5$ Hz, 2H), 7.13 (t, $J = 7.7$ Hz, 1H), 6.79 (d, $J = 7.7$ Hz, 1H), 6.66 (t, $J = 7.7$ Hz, 1H), 6.23 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.41, 149.82, 142.67, 140.01, 138.85, 134.41, 133.86, 132.11, 131.16, 129.94, 129.85, 128.26, 126.14, 123.27, 123.15, 121.19, 110.10; MS (ESI) m/z : 366 $[M + H]^+$.

3-((4-Chlorophenyl)(2,4-dichlorophenyl)methylene)indolin-2-one. Yellow crystals in 83% yield. *E*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.60 (s, 1H), 7.86 (d, $J = 2.0$ Hz, 1H), 7.62 (dd, $J = 8.3, 2.1$ Hz, 1H), 7.53 (d, $J = 8.3$ Hz, 1H), 7.40 (s, 4H), 7.16 (t, $J = 7.7$ Hz, 1H), 6.80 (d, $J = 7.7$ Hz, 1H), 6.70 (t, $J = 7.6$ Hz, 1H), 5.92 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.01, 145.65, 142.81, 138.45, 136.69, 134.92, 133.92, 132.80, 131.95, 131.90, 130.48, 130.42, 129.24, 128.16, 127.39, 123.00, 122.95, 121.67, 110.21; MS (ESI) m/z : 400 $[M + H]^+$. *Z*-isomer: 10.58 (s, 1H), 7.65 (d, $J = 2.0$ Hz, 1H), 7.58 (d, $J = 8.6$ Hz, 2H), 7.47 (d, $J = 8.6$ Hz, 2H), 7.44 (d, $J = 2.0$ Hz, 1H), 7.42 (s, 1H), 7.19 (td, $J = 7.7, 1.1$ Hz, 1H), 6.82 (d, $J = 7.6$ Hz, 1H), 6.73 (td, $J = 7.7, 1.0$ Hz, 1H), 6.50 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.15, 144.82, 143.20, 138.97, 137.89, 134.46, 133.47, 132.89, 131.74, 130.72, 129.76, 129.31, 128.10, 128.01, 123.32, 121.94, 121.43, 110.39; MS (ESI) m/z : 400 $[M + H]^+$.

3-((4-Hydroxyphenyl)(phenyl)methylene)indolin-2-one. Yellow crystals in 77% total yield. *E*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.40 (s, 1H), 9.93 (s, 1H), 7.36–7.29 (m, 3H), 7.23 (dd, $J = 7.6, 1.8$ Hz, 2H), 7.10–7.05 (m, 3H), 6.85 (d, $J = 8.5$ Hz, 2H), 6.77 (d, $J = 7.7$ Hz, 1H), 6.64 (t, $J = 7.6$ Hz, 1H), 6.44 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.81, 159.06, 154.09, 142.11, 140.90, 132.15, 131.44, 130.69, 129.04, 128.97, 127.98, 124.31, 124.27, 122.70, 120.82, 116.22, 109.75; MS (ESI) m/z : 314 $[M + H]^+$. *Z*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.42 (s, 1H), 9.82 (s, 1H), 7.51–7.46 (m, 3H), 7.26–7.21 (m, 2H), 7.13 (d, $J = 8.6$ Hz, 2H), 7.03 (td, $J = 7.7, 1.0$ Hz, 1H), 6.75 (d, $J = 7.6$ Hz, 1H), 6.71 (d, $J = 8.7$ Hz, 2H), 6.52 (t, $J = 7.7$ Hz, 1H), 5.95 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.76, 159.28, 154.19, 142.19, 141.80, 133.06, 130.29, 129.52, 128.62, 124.59, 123.49, 122.73, 120.69, 114.79, 109.64; MS (ESI) m/z : 314 $[M + H]^+$.

3-((4-Methoxyphenyl)(phenyl)methylene)indolin-2-one. Yellow crystals in 73% total yield. *E*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.42 (s, 1H), 7.35–7.30 (m, 3H), 7.25–7.21 (m, 2H), 7.19 (d, $J = 8.7$ Hz, 2H), 7.09 (td, $J = 7.7, 0.9$ Hz, 1H), 7.04 (d, $J = 8.7$ Hz, 2H), 6.77 (d, $J = 7.7$ Hz, 1H), 6.63 (td, $J = 7.7, 0.7$ Hz, 1H), 6.37 (d, $J = 7.7$ Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.71, 160.48, 153.42, 142.24, 140.78, 133.78, 131.21, 130.57, 129.17, 129.04, 128.02, 124.68, 124.11, 122.75, 120.89, 114.88, 109.81, 55.73; MS (ESI) m/z : 328 $[M + H]^+$. *Z*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.45 (s, 1H), 7.54–7.45 (m, 3H), 7.28–7.21 (m, 4H), 7.05 (td, $J = 7.7, 1.1$ Hz, 1H), 6.89 (d, $J = 8.9$ Hz, 2H), 6.76 (d, $J = 7.5$ Hz, 1H), 6.55 (td, $J = 7.7, 1.0$ Hz, 1H), 6.00 (d, $J = 7.7$ Hz, 1H), 3.79 (s, 3H); ^{13}C NMR

(101 MHz, DMSO- d_6) δ (ppm): 167.70, 160.55, 153.48, 142.05, 132.68, 132.02, 129.58, 129.56, 129.40, 128.93, 124.32, 124.14, 122.84, 120.77, 113.40, 109.73, 55.63; MS (ESI) m/z : 328 $[M + H]^+$.

3-((4-Chlorophenyl)(*m*-tolyl)methylene)indolin-2-one. Yellow crystals in 83% total yield. *E*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.50 (s, 1H), 7.41–7.36 (m, 3H), 7.32–7.28 (m, 3H), 7.12–7.07 (m, 3H), 6.78 (d, $J = 7.7$ Hz, 1H), 6.59 (td, $J = 7.7, 1.0$ Hz, 1H), 6.14 (d, $J = 7.7$ Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.57, 151.64, 142.50, 141.27, 139.10, 133.67, 131.97, 130.22, 129.65, 129.62, 129.17, 128.17, 125.99, 125.64, 123.57, 123.23, 121.03, 109.95, 21.37; MS (ESI) m/z : 346 $[M + H]^+$. *Z*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.48 (s, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.22 (t, $J = 7.7$ Hz, 1H), 7.18–7.04 (m, 4H), 6.79 (d, $J = 7.7$ Hz, 1H), 6.65 (t, $J = 7.6$ Hz, 1H), 6.19 (d, $J = 7.7$ Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.40, 151.79, 142.51, 140.52, 140.10, 137.19, 134.19, 131.04, 130.41, 129.76, 129.66, 128.13, 127.39, 125.57, 123.49, 123.01, 121.08, 109.99, 21.41; MS (ESI) m/z : 346 $[M + H]^+$.

3-((4-Hydroxyphenyl)(*m*-tolyl)methylene)indolin-2-one. Yellow crystals in 80% total yield. *E*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.39 (s, 1H), 9.79 (s, 1H), 7.37 (t, $J = 7.7$ Hz, 1H), 7.31 (d, $J = 7.4$ Hz, 1H), 7.12 (d, $J = 8.6$ Hz, 2H), 7.06–7.00 (m, 3H), 6.74 (d, $J = 7.5$ Hz, 1H), 6.70 (d, $J = 8.7$ Hz, 2H), 6.54 (td, $J = 7.7, 1.0$ Hz, 1H), 5.99 (d, $J = 7.7$ Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.77, 159.25, 154.37, 142.17, 141.75, 138.81, 133.01, 130.29, 130.13, 129.79, 129.40, 128.57, 126.58, 124.64, 123.35, 122.76, 120.70, 114.77, 109.60, 21.38; MS (ESI) m/z : 328 $[M + H]^+$. *Z*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.36 (s, 1H), 9.90 (s, 1H), 7.24–7.13 (m, 2H), 7.09–6.99 (m, 5H), 6.84 (d, $J = 8.2$ Hz, 2H), 6.76 (d, $J = 7.6$ Hz, 1H), 6.63 (t, $J = 7.5$ Hz, 1H), 6.42 (d, $J = 7.6$ Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.79, 159.04, 154.31, 142.05, 140.96, 136.92, 132.14, 131.40, 130.94, 129.73, 128.91, 127.91, 127.88, 124.33, 124.20, 122.63, 120.79, 116.20, 109.72, 21.41; MS (ESI) m/z : 328 $[M + H]^+$.

3-((4-Chlorophenyl)(*p*-tolyl)methylene)indolin-2-one. Yellow crystals in 79% total yield. *E*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.48 (s, 1H), 7.55 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.18–7.07 (m, 5H), 6.77 (d, $J = 7.7$ Hz, 1H), 6.64 (t, $J = 7.7$ Hz, 1H), 6.18 (d, $J = 7.7$ Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.48, 151.85, 142.38, 140.67, 138.95, 137.02, 134.24, 131.30, 130.57, 129.71, 129.49, 128.75, 125.21, 123.71, 122.94, 121.03, 109.94, 21.42; MS (ESI) m/z : 346 $[M + H]^+$. *Z*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.51 (s, 1H), 7.37 (d, $J = 8.5$ Hz, 2H), 7.30 (d, $J = 7.9$ Hz, 2H), 7.26 (d, $J = 8.5$ Hz, 2H), 7.17 (d, $J = 8.0$ Hz, 2H), 7.09 (t, $J = 7.7$ Hz, 1H), 6.78 (d, $J = 7.7$ Hz, 1H), 6.61 (t, $J = 7.6$ Hz, 1H), 6.28 (d, $J = 7.7$ Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.63, 151.69, 142.46, 139.38, 138.37, 133.72, 132.17, 130.22, 129.58, 129.23, 128.13, 125.48, 123.68, 123.06, 120.99, 109.95, 21.43; MS (ESI) m/z : 346 $[M + H]^+$.

3-((4-Hydroxyphenyl)(*p*-tolyl)methylene)indolin-2-one. Yellow crystals in 72% total yield. *E*-isomer: 1H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.38 (s, 1H), 9.92 (s, 1H), 7.12 (s, 4H), 7.08–7.03 (m, 3H), 6.84 (d, $J = 8.6$ Hz, 2H), 6.76 (d, $J = 7.6$ Hz, 1H), 6.62 (t, $J = 8.1$ Hz, 1H), 6.40 (d, $J = 7.7$ Hz, 1H), 2.33 (s, 3H); ^{13}C NMR



NMR (101 MHz, DMSO- d_6) δ (ppm): 167.89, 159.10, 154.38, 141.90, 138.88, 137.87, 132.26, 131.65, 131.03, 128.73, 128.58, 124.57, 123.79, 122.57, 120.75, 116.17, 109.68, 21.44; MS (ESI) m/z : 328 [M + H]⁺. *Z*-isomer: ¹H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.38 (s, 1H), 9.79 (s, 1H), 7.29 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 7.02 (t, J = 7.2 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.70 (d, J = 8.6 Hz, 2H), 6.55 (t, J = 7.3 Hz, 1H), 6.11 (d, J = 7.7 Hz, 1H), 2.39 (s, 3H); ¹³C NMR (101 MHz, DMSO- d_6) δ (ppm): 167.83, 159.30, 154.43, 141.69, 139.24, 133.19, 130.57, 130.03, 129.80, 128.49, 124.74, 123.17, 122.58, 120.67, 114.75, 109.60, 21.45; MS (ESI) m/z : 328 [M + H]⁺.

General procedure for alkylation of alkene oxindole compounds with 3-(bromomethyl)benzoic acid methyl ester exemplified by the isomer mixture of 3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one

Isomer mixture of 3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one (2 g, 0.006 mol) and potassium carbonate (2.5 g, 0.018 mol) were dissolved in 100 mL dimethylformamide, and methyl 3-(bromomethyl)benzoate (2 g, 0.007 mol) dissolved in dimethylformamide was added gradually for an hour. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure, and then water was added to the residue. The precipitate was filtered off, dissolved in ethyl acetate, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The product mixture was purified by flash chromatography (*n*-hexane/ethyl acetate 9 : 1).

3-((3-((4-Chlorophenyl)(phenyl)methylene)-2-oxoindolin-1-yl)methyl)benzoic acid methyl ester. Yellow crystals in 93% total yield. Spectral characteristics for *E*-isomer are given above (C24 synthesis). *Z*-isomer: ¹H NMR (400 MHz, DMSO- d_6) δ (ppm): 7.96 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.50–7.54 (m, 3H), 7.48 (t, J = 7.7 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.31–7.36 (m, 4H), 7.11 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.65 (t, J = 7.6 Hz, 1H), 6.22 (d, J = 7.7 Hz, 1H), 4.97 (s, 2H), 3.86 (s, 3H); MS (ESI) m/z : 480 [M + H]⁺.

General procedure for alkaline hydrolysis for esters of N-alkylated alkene oxindole compounds

Lithium hydroxide (1.2 g, 0.05 mol) dissolved in 50 mL water was added to the corresponding methyl ester (2.4 g, 0.005 mol) dissolved in 50 mL THF. The reaction mixture was stirred at rt and monitored by TLC. Then the mixture was acidified with 15% HCl and THF was almost completely distilled from the aqueous mixture. After THF was removed, the formed precipitate was filtered off, washed with 50 mL water and dried. The crude product was purified by recrystallization from ethyl acetate.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by the Russian Science Foundation (project no. 16-13-10358). XRD studies were performed at the Centre for X-ray Diffraction Methods of Research park of St. Petersburg State University.

Notes and references

- (a) G. R. Steinberg and B. E. Kemp, *Physiol. Rev.*, 2009, **89**, 1025; (b) D. G. Hardie and M. L. Ashford, *Physiology*, 2014, **29**, 99.
- (a) D. G. Hardie, *Diabetes*, 2013, **62**, 2164; (b) E. A. Day, R. J. Ford and G. R. Steinberg, *Trends Endocrinol. Metab.*, 2017, **28**, 545.
- (a) L. G. Fryer, A. Parbu-Patel and D. Carling, *J. Biol. Chem.*, 2002, **277**, 25226; (b) D. G. Hardie, F. A. Ross and S. A. Hawley, *Chem. Biol.*, 2012, **19**, 1222.
- D. S. Novikova, A. V. Garabadzhiu, G. Melino, N. A. Barlev and V. G. Tribulovich, *Russ. Chem. Bull.*, 2015, **64**, 1497.
- (a) J. E. Sullivan, K. J. Brocklehurst, A. E. Marley, F. Carey, D. Carling and R. K. Beri, *FEBS Lett.*, 1994, **353**, 33; (b) N. Henin, M. F. Vincent and G. Van den Berghe, *Biochim. Biophys. Acta*, 1996, **1290**, 197; (c) C. G. Langendorf, K. R. Ngoei, J. W. Scott, N. X. Ling, S. M. Issa, M. A. Gorman, M. W. Parker, K. Sakamoto, J. S. Oakhill and B. E. Kemp, *Nat. Commun.*, 2016, **7**, 10912.
- (a) B. Cool, B. Zinker, W. Chiou, L. Kifle, N. Cao, M. Perham, R. Dickinson, A. Adler, G. Gagne, R. Iyengar, G. Zhao, K. Marsh, P. Kym, P. Jung, H. S. Camp and E. Frevert, *Cell Metab.*, 2006, **3**, 403; (b) G. Zhao, R. R. Iyengar, A. S. Judd, B. Cool, W. Chiou, L. Kifle, E. Frevert, H. Sham and P. R. Kym, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3254.
- (a) J. Charton, S. Girault-Mizzi, M. A. Debreu-Fontaine, F. Fougelle, I. Hainault, J. G. Bizot-Espiard, D. H. Caignard and C. Sergheraert, *Bioorg. Med. Chem.*, 2006, **14**, 4490; (b) B. C. Bookser, Q. Dang, T. S. Gibson, H. Jiang, D. M. Chung, J. Bao, J. Jiang, A. Kassick, A. Kekec, P. Lan, H. Lu, G. Makara, F. A. Romero, I. Sebhat, D. Wilson and D. Wodka, *US Pat.*, 8394969B2, 2013.
- L. F. Yu, Y. Y. Li, M. B. Su, M. Zhang, W. Zhang, L. N. Zhang, T. Pang, R. T. Zhang, B. Liu, J. Y. Li, J. Li and F. J. Nan, *ACS Med. Chem. Lett.*, 2013, **4**, 475.
- C. G. Langendorf and B. E. Kemp, *Cell Res.*, 2015, **25**, 5.
- (a) A. Millemaggi and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2010, **24**, 4527; (b) Z. Y. Cao, F. Zhou and J. Zhou, *Acc. Chem. Res.*, 2018, **51**, 1443.
- (a) G. H. Zheng, J. J. Shen, Y. C. Zhan, H. Yi, S. T. Xue, Z. Wang, X. Y. Ji and Z. R. Li, *Eur. J. Med. Chem.*, 2014, **81**, 277; (b) A. Pal, A. Ganguly, A. Ghosh, M. Yousuf, B. Rathore, R. Banerjee and S. Adhikari, *ChemMedChem*, 2014, **9**, 727.
- P. Li, M. Zhao, A. B. Parris, X. Feng and X. Yang, *Biochem. Biophys. Res. Commun.*, 2015, **464**, 1267.
- (a) T. A. Grigoreva, D. S. Novikova, M. A. Gureev, A. V. Garabadzhiu and V. G. Tribulovich, *Chirality*, 2018, **30**, 785; (b) T. A. Grigoreva, D. S. Novikova, A. V. Petukhov,



- M. A. Gureev, A. V. Garabadzhiu, G. Melino, N. A. Barlev and V. G. Tribulovich, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 5197; (c) T. A. Grigoreva, A. V. Garabadzhiu and V. G. Tribulovich, *Russ. J. Gen. Chem.*, 2016, **86**, 2454.
- 14 J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369.
- 15 F. Nan, L. Yu, M. Zhang, L. Chen, M. Huang, L. Feng, J. Li and T. Pang, *US Pat.*, 8778973B2, 2014.
- 16 (a) A. Pinto, L. Neuville, P. Retailleau and J. Zhu, *Org. Lett.*, 2006, **8**, 4927; (b) D. Lee, S. Park, Y. Yu, K. J. Shin and J. H. Seo, *Molecules*, 2015, **20**, 14022; (c) S. Park, J. Lee, K. J. Shin, E. Oh and J. H. Seo, *Molecules*, 2017, **22**, 503.
- 17 (a) F. Hu, P. Nareddy, R. Lalancette, F. Jordan and M. Szostak, *Org. Lett.*, 2017, **19**, 2386; (b) F. Hu, R. Lalancette and M. Szostak, *Angew. Chem., Int. Ed.*, 2016, **55**, 5062.
- 18 T. P. Du, G. G. Zhu and J. Zhou, *Lett. Org. Chem.*, 2012, **9**, 225.
- 19 B. A. Robichaud and K. G. Liu, *Tetrahedron Lett.*, 2011, **52**, 6935.
- 20 H. J. Lee, J. W. Lim, J. Yu and J. N. Kim, *Tetrahedron Lett.*, 2014, **55**, 1183.
- 21 F. Texier-Boullet and A. Foucaud, *Tetrahedron Lett.*, 1982, **23**, 4927.
- 22 L. Sun, N. Tran, F. Tang, H. App, P. Hirth, G. McMahon and C. Tang, *J. Med. Chem.*, 1998, **41**, 2588.
- 23 (a) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900; (b) F. Roudesly, J. Oble and G. Poli, *J. Mol. Catal. A: Chem.*, 2017, **426 B**, 275.
- 24 C. Crestini and R. Saladino, *Synth. Commun.*, 1994, **24**, 2835.

