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Graphical Abstract

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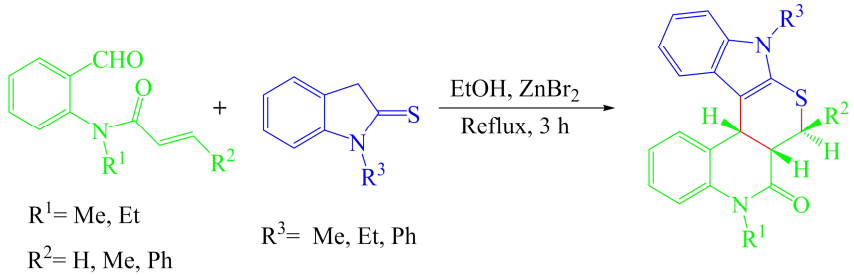


R^1= Me, Et

R^2= H, Me, Ph

R^3= Me, Et, Ph

$ZnBr_2$ catalyzed domino Knoevenagel-hetero-Diels–Alder reaction: an efficient route to polycyclic thiopyranoindol annulated [3,4-c]quinolone derivatives

Mostafa Kiamehr [a,*], Batoul Alipour [a], Leyla Mohammadkhani [a], Behzad Jafari [b], Peter Langer [b,c]

[a] *Department of Chemistry, Faculty of Science, University of Qom, Ghadir Blvd, P.O. Box 37146-6611, Qom, Iran*

[b] *Institut für Chemie der Universität Rostock, Albert-Einstein-Straße 3a, D-18059 Rostock, Germany*

[c] *Leibniz Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Straße 29a, D-18059 Rostock, Germany*

*Corresponding author. Tel.: +98-25-32103093

E-mail address: mkiamehr@yahoo.com, m.kiamehr@qom.ac.ir

Abstract. Various novel polycyclic thiopyranoindol annulated [3,4-c]quinolone derivatives were synthesized via domino Knoevenagel-hetero-Diels–Alder reactions of indoline-2-thions and novel *N*-acrylated anthranilaldehydes in refluxing ethanol as a solvent in the presence of 20 mol% $ZnBr_2$ as a Lewis acid catalyst. All reactions proceed with high yields with excellent regio- and stereoselectivity.

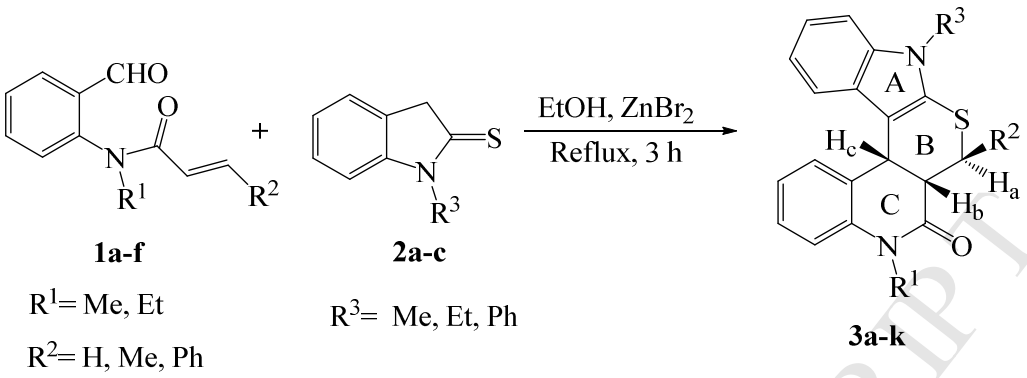
Keywords: Domino reaction, Knoevenagel-hetero-Diels–Alder, Indole, Indolin-2-thione, 3,4-Dihydroquinolone, $ZnBr_2$ catalyzed

1. Introduction

Indole derivatives are important heterocycles. They are widespread in nature and have various biological activities,[1] such as topical anti-inflammatory,[2] anti-HIV[3] and antitumor activities.[4] Also compounds possessing tetrahydrothiopyrano indole moieties are very important because of their different biological and medicinal activities.[5] On the other hand, the dihydroquinolone (3,4-dihydroquinolin-2-one) structure is found in many pharmacologically important natural products and synthetic compounds.[6] Simple alkoxydihydroquinolones form the core of the commercial drugs such as carteolol,[7] cilostazol[8] and aripiprazole.[9] Many 3,4-disubstituted

dihydroquinolones have cardiovascular, anti-inflammatory and phosphodiesterase inhibitory activities.[10] The 3,4-dihydroquinolone structure is also embedded within pentacyclic alkaloids of the Melodinus scandens family, exemplified by scandine, meloscine and epimeloscine,[11] as well as the structurally unique alkaloids of the Trigolutesin A,[12] scandomelonine and episcandomelonine that have both indole and 3,4-dihydroquinolone moieties.[11b] Not surprisingly, methods for the synthesis of 3,4-disubstituted dihydroquinolones have attracted significant attention. Protocols, such as Friedlander/Friedel–Crafts cyclization,[13] Skraup–Doebner–Von Miller reaction,[14] oxidative cyclization,[15] radical reactions,[16] photocyclizations,[17] palladium-catalyzed cyclocarbonylation[18] and rhodium-catalyzed reaction[19] approaches have been reported. Despite their efficiencies, most of the reported reactions are either multi-step, or are not suited for the synthesis of 3,4-disubstituted dihydroquinolones containing other heterocyclic groups.

The domino Knoevenagel-hetero-Diels–Alder (DKHDA) reaction is a popular strategy for the synthesis of polycyclic heterocycles and natural products.[20] A wide range of heterocyclic compounds, especially polycycles with a pyran or chroman moiety have been synthesized by domino-Knoevenagel-hetero-Diels–Alder reaction.[21] In addition there are some reports of domino-Knoevenagel-hetero-Diels–Alder reactions for the synthesis of polycycles with a benzosultone or benzosultam moiety.[22] In this regard, previously we reported domino Knoevenagel-hetero-Diels–Alder reactions of *O*-acrylated salicylaldehyde derivatives for synthesis of pentacycles with a dihydrocoumarin ring.[23] The goal of the present study was to introduce a new methodology for synthesis of pentacyclic heterocycles with 3,4-disubstituted dihydroquinolones, in one step. To the best of our knowledge, this is the first example of using *N*-acrylated anthranilaldehydes in the domino Knoevenagel-hetero-Diels–Alder reaction with indolin-2-thiones. In the context of our general interest in the domino Knoevenagel-hetero-Diels–Alder reactions,[21a,22b,23] and synthesis of heterocyclic compounds using indolin-2-thiones,[24] we herein report a new and highly efficient reaction for the preparation of pentacyclic compounds **3a-k**, which consist of an indole ring (A), a tetrahydrothiopyran ring (B) annulated to a 3,4-dihydroquinolone ring (C) (Scheme 1).



1a-f

R^1= Me, Et

R^2= H, Me, Ph

2a-c

R^3= Me, Et, Ph

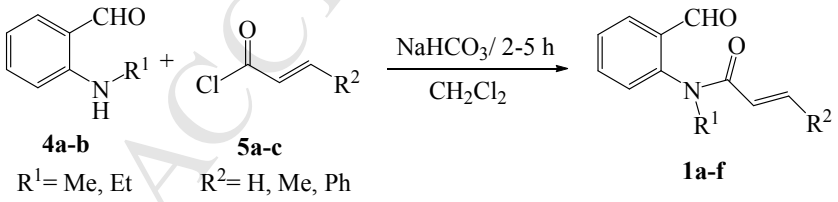
3a-k

Scheme 1.

2. Results and discussion

2.1. Preparation of *N*-acrylated anthranilaldehyde derivatives for domino Knoevenagel-hetero-Diels–Alder reaction

N-alkylanthranilaldehydes **4a-b** were prepared from the corresponding *N*-alkylquinoline salts on the basis of the previously reported method.[25] *N*-acrylated anthranilaldehyde derivatives **1a-f** were then prepared from condensation of *N*-alkylanthranilaldehydes **4a-b** and (*E*)-acryloyl chloride derivatives (acryloyl chloride, (*E*)-crotonoyl chloride and (*E*)-cinnamoyl chloride) **5a-c** in the presence of $NaHCO_3$ in CH_2Cl_2 within 2-5 h in good yields (Scheme 2). *N*-Acrylatedanthranilaldehyde derivatives **1a-f** were completely characterized using their analytical and spectral data. For example, the ^{1}H NMR spectrum of **1c** exhibited characteristic singlet at δ 3.37 ppm for NMe followed by two doublet at 6.05 and 7.64 for the =CH (J = 15.4 Hz) in *trans*-relation with each other, together with a singlet at 10.05 due to CHO.



4a-b

R^1= Me, Et

5a-c

R^2= H, Me, Ph

1a-f

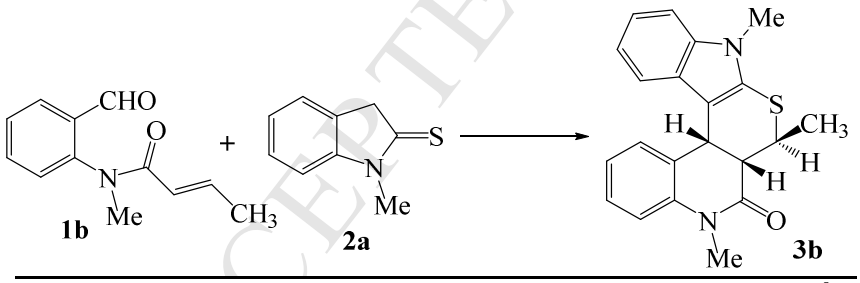
	R^1	R^2	Yield (%)
1a	Me	H	85
1b	Me	Me	80
1c	Me	Ph	76
1d	Et	H	78
1e	Et	Me	73
1f	Et	Ph	65

Scheme 2.

2.2. Domino Knoevenagel-hetero-Diels–Alder reaction of *N*-acrylated anthranilaldehyde derivatives with indolin-2-thiones

To optimize the reaction conditions, we screened the domino Knoevenagel-hetero-Diels–Alder reaction of compound **1b** with 1-methylindoline-2-thione **2a** as a model. The effect of several solvents and catalysts were studied (Table 1). Using refluxing water or acetonitrile as a solvent under catalyst-free conditions for 24 h, the products were obtained in 10% and 12% yield respectively (Entries 1 and 2, Table 1). When the reaction was carried out in the presence of ZnO as a Lewis acid in acetonitrile for 24 h at refluxing temperature, the yield was increased to 35% (Entry 3). The effect of other solvents in the presence of ZnO was studied. Using MeOH and EtOH as solvents did not give the significant influence to the yield of product (Entries 4 and 5). Surprisingly the addition of $ZnBr_2$ as a catalyst and ethanol as solvent dramatically increased the yield of reaction to 88% and decreased the time of reaction to 3 hours (Entry 6). Decreasing the ratio of $ZnBr_2$ to 50 mol% and 20 mol% afforded the same results, but with 10 mol% of $ZnBr_2$ in the same times, gave lower yield (Entries 7, 8 and 9). We also examined other conditions, for example Lewis base (Entry 10) or $ZnCl_2$ (Entry 11), also we checked $ZnBr_2$ in water (Entry 12), but the best conditions was entry 9. In all the cases the product was obtained as a *cis* isomer.

Table 1
Effect of catalysts and solvents on the domino Knoevenagel-hetero-Diels–Alder reaction of compounds **1b** and **2a**



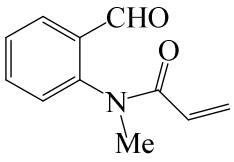
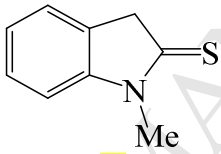
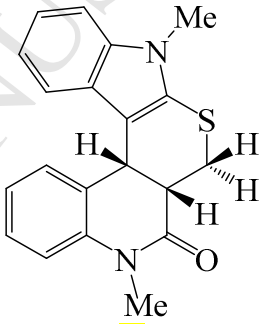
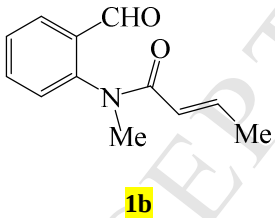
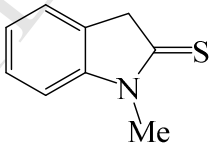
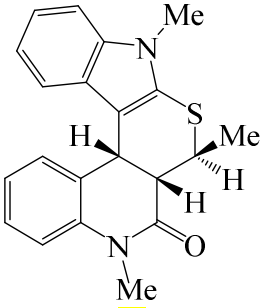
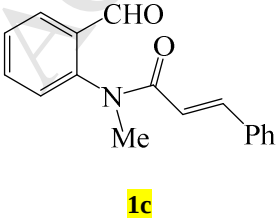
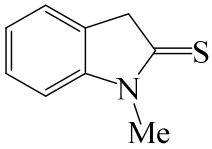
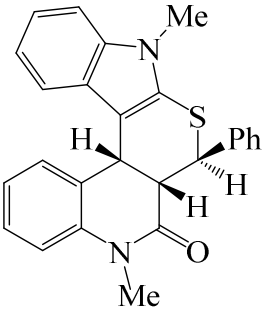
Entry	Solvent	Catalyst	Temp. (°C)	Time (h)	Yield[a] (%)
1	H_2O	-	Reflux	24	10
2	CH_3CN	-	Reflux	24	12
3	CH_3CN	ZnO (100%)	Reflux	24	35
4	MeOH	ZnO (100%)	Reflux	24	30
5	EtOH	ZnO (100%)	Reflux	24	48
6	EtOH	$ZnBr_2$ (100%)	Reflux	3	88
7	EtOH	$ZnBr_2$ (50%)	Reflux	3	88
8	EtOH	$ZnBr_2$ (20%)	Reflux	3	88
9	EtOH	$ZnBr_2$ (10%)	Reflux	3	68
10	EtOH	Et_3N	Reflux	24	0

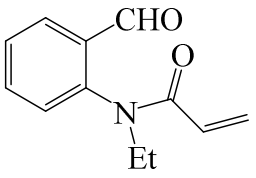
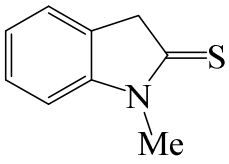
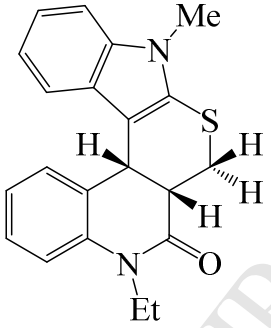
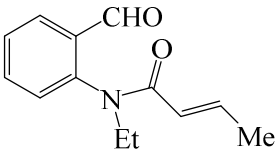
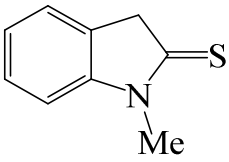
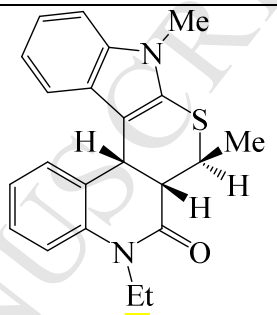
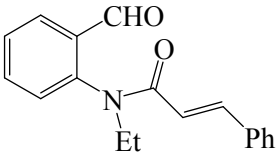
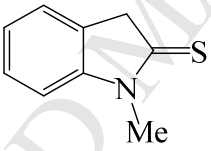
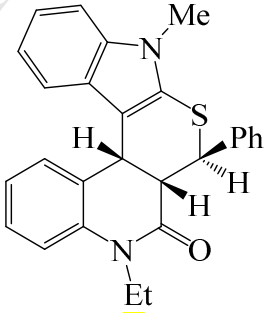
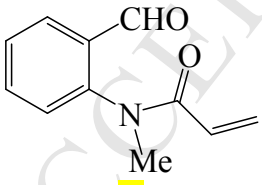
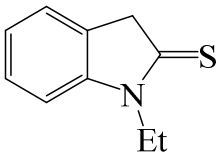
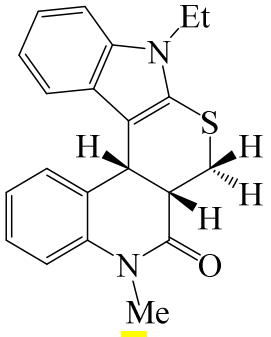
11	EtOH	$ZnCl_2$ (20%)	Reflux	24	60
12	H_2O	$ZnBr_2$ (20%)	Reflux	24	22

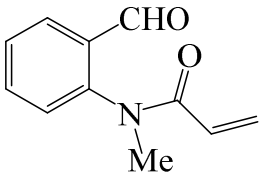
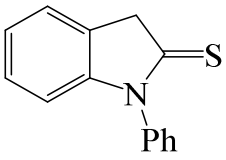
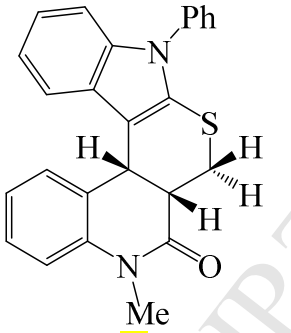
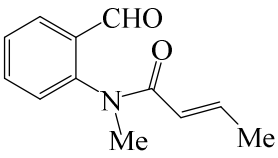
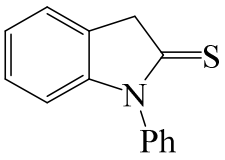
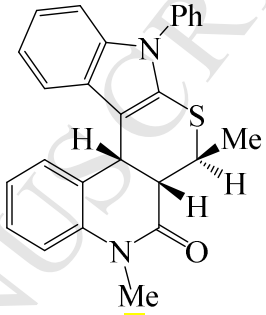
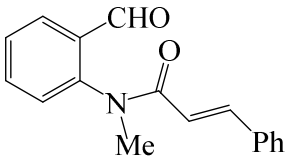
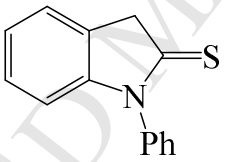
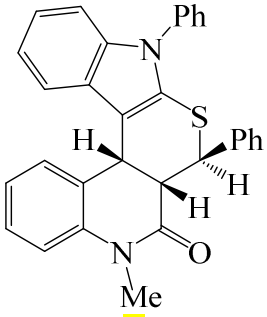
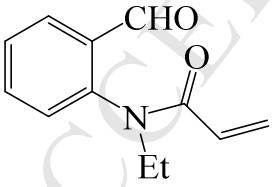
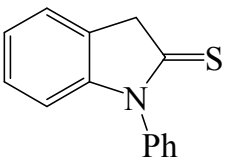
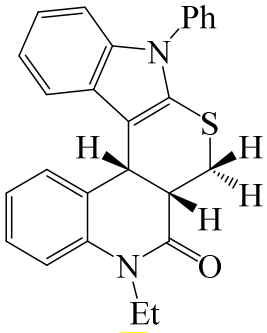
[a] Yield of isolated products.

Under the optimized conditions, we next investigated the effect of substitutions on the yield as well as regio- and stereoselectivity of domino Knoevenagel-hetero-Diels–Alder reaction of *N*-acrylated anthranilaldehyde derivatives **1a-f** and indoline-2-thiones **2a–c** (Table 2).

Table 2
Domino Knoevenagel-hetero-Diels–Alder reactions of *N*-acrylated anthranilaldehyde derivatives **1a-f** with indoline-2-thiones **2a-c**[a]

Entry	Aldehydes **1**	Indoline-2-thiones **2**	Products **3**	Yield[b]
1	 **1a**	 **2a**	 **3a**	90
2	 **1b**	 **2a**	 **3b**	88
3	 **1c**	 **2a**	 **3c**	95

4	 **1d**	 **2a**	 **3d**	87
5	 **1e**	 **2a**	 **3e**	83
6	 **1f**	 **2a**	 **3f**	92
7	 **1a**	 **2b**	 **3g**	90

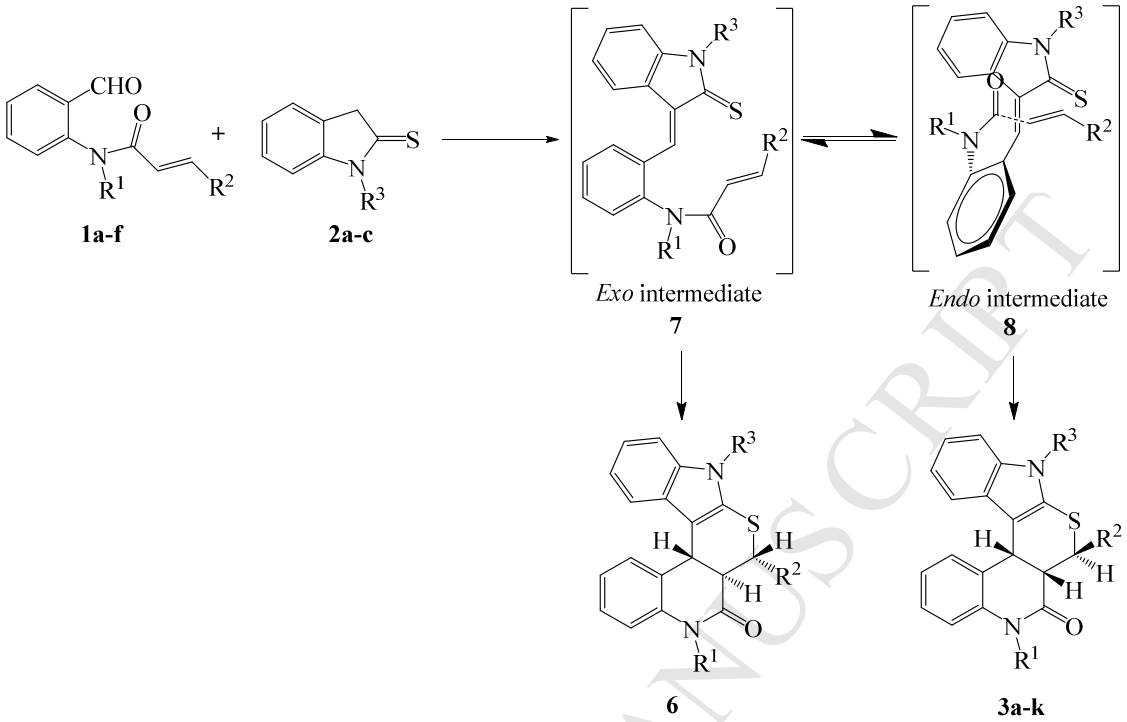
8	 **1a**	 **2c**	 **3h**	85
9	 **1b**	 **2c**	 **3i**	90
10	 **1c**	 **2c**	 **3j**	94
11	 **1d**	 **2c**	 **3k**	87

[a] All the reactions were carried out at reflux in the EtOH for 3 h in the presence of $ZnBr_2$ (20 mol%).
[b] Isolated products.

The structures of the products **3a-k** were established on the basis of their spectral data (^{1}H and ^{13}C NMR, DEPT and IR), as well as HRMS analysis. The

relative configurations were determined from the coupling constants of the relevant H-atoms and also by direct comparison with the reported data in literature.[20-23] For instance, the characteristic peaks for **3b** in the ^{1}H NMR spectra are a doublet of doublet (J = 9.6, 4.6 Hz) at δ 2.99 ppm for the H_b followed by a multiplet for the H_a at δ 3.48-3.59 ppm and a doublet for the H_c with J = 4.5 Hz at δ 4.71 ppm that show *trans*-relation between H_a and H_b also *cis*-relation between H_a and H_c respectively. In all the synthesized products, the relative orientations of the H-atoms were found to be same.

A plausible mechanism for the domino Knoevenagel-hetero-Diels–Alder reaction is shown in Scheme 3. Initially aldehydes **1** undergo a Knoevenagel condensation with indolin-2-thiones **2** in the presence of $ZnBr_2$ ($ZnBr_2$ as a Lewis acid can facilitate the condensation) to afford an alkene intermediate, which has not been isolated. The stereochemistry of the final products depends on the *endo*- and *exo*-orientation of the dienophile in the transition state. We assume that the *trans*-cycloadducts **6** could form via an *exo*-transition state (intermediates **7**), whereas the *cis*-isomers **3a-k** resulted from an *endo*-transition state (intermediates **8**), as represented in Scheme 3. Here only the products **3a-k** were isolated which shows that the *endo*-transition states are more stable than *exo*-transition states, due to secondary orbital interaction, so reactions proceed via intermediates **8** to produce the *cis*-isomers **3a-k** with excellent regio- and stereoselectivity.



Scheme 3. A plausible mechanism for the formation of compounds **3a-k**.

3. Conclusion

We have reported a $ZnBr_2$-catalyzed domino Knoevenagel-intramolecular-hetero-Diels–Alder reaction of novel *N*-acrylated anthranilaldehydes and indoline-2-thions with high efficiency and excellent regio- and stereoselectivity to provide various novel pentacyclic thiopyranoindol annulated [3,4-c]quinolone derivatives in a single step.

The major advantages of this reaction are the ease of the work-up (products can be isolated without chromatography), clean reactions, high yields of products, short reaction times, in the presence of 20 mol% $ZnBr_2$ as a commercially available and inexpensive catalyst, which make it a useful and attractive strategy for the synthesis of quinolone-indole hybrids.

4. Experimental section

4.1. General

Commercially available materials were used without any additional purification. Analytical thin layer chromatography was performed on 0.20 mm 60 A silica gel plates. Column chromatography was performed using 60 A silica gel (60–200 mesh). Infrared spectra were recorded in an ATR apparatus. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). Melting points are uncorrected. ^{1}H NMR, ^{13}C NMR and DEPT spectra in $CDCl_3$ at r.t.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz.

4.2. General procedure for preparation of the *N*-acrylated anthranilaldehyde derivatives 1a-f

To a stirred solution of *N*-alkylanthranilaldehydes **4** (10 mmol) and sodium bicarbonate ($NaHCO_3$) (15 mmol) in dry CH_2Cl_2 (15 mL) at 0-5 °C, was added dropwise a solution of acryloyl chloride derivatives **5** (12 mmol) in dry CH_2Cl_2 (15 mL) at 0-5 °C, over 45 minutes, which was then stirred at room temperature to 2-5 h. The organic solution was then washed with water (20 mL) and hydrogen chloride (5%) solution (20 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was separated by column chromatography on a silica gel with petroleum ether/ethyl acetate (3:1) as an eluent to obtain pure *N*-acrylated anthranilaldehyde derivatives **1a-f**.

4.2.1. *N-(2-Formylphenyl)-N-methylacrylamide (**1a**)*. Light brown liquid, yield 85% (1.61 g). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.32 (3H, s, NCH_3), 5.47 (1H, dd, *J* = 10.3, 1.8 Hz), 5.80 (1H, dd, *J* = 16.7, 10.3 Hz), 6.33 (1H, dd, *J* = 16.7, 1.8 Hz), 7.23 (1H, dd, *J* = 8.0, 0.9 Hz, Ar-H), 7.47(1H, t, *J* = 7.7 Hz, Ar-H), 7.64 (1H, td, *J* = 7.7, 1.6 Hz, Ar-H), 7.92 (1H, dd, *J* = 7.7, 1.6 Hz, Ar-H), 10.00 (1H, s, -CHO); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 38.3 (NCH_3), 127.6 (CH), 128.9 (CH), 129.0 (CH_2), 129.3 (CH), 129.9 (CH), 132.7 (C), 135.6 (CH), 145.2 (C), 165.9 (CON), 189.1 (CHO). IR (ATR, cm^{-1}): ῡ= 3066, 2928, 2852, 2750, 1692, 1652, 1594, 1398, 1349, 1262, 1192, 773. HRMS (ESI): calcd for $C_{11}H_{11}O_2N_1$ (M^+) 189.0784, found 189.0782.

4.2.2. *(E)-N-(2-Formylphenyl)-N-methylbut-2-enamide (**1b**)*. Light brown liquid, yield 80% (1.625 g). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.70 (3H, dd, *J* = 6.9, 1.5 Hz, CH_3), 3.37 (3H, s, NCH_3), 5.53 (1H, dq, *J* = 15.0, 1.5 Hz), 6.90-

7.05 (1H, m), 7.30 (1H, dd, *J* = 7.5, 0.7 Hz, Ar-H), 7.53 (1H, t, *J* = 7.5 Hz, Ar-H), 7.70 (1H, td, *J* = 7.8, 1.5 Hz, Ar-H), 7.99 (1H, dd, *J* = 7.8, 1.5 Hz, Ar-H), 10.07 (1H, s, -CHO); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 18.0 (CH_3), 38.2 (NCH_3), 121.9 (CH), 128.7 (CH), 129.3 (CH), 129.5 (CH), 132.8 (C), 135.5 (CH), 143.2 (CH), 145.8 (C), 166.3 (CON), 189.3 (CHO). IR (ATR, cm^{-1}): ῡ= 3055, 2916, 2851, 2750, 1692, 1661, 1629, 1593, 1445, 1370, 1191, 1089, 963, 773, 568. HRMS (ESI): calcd for $C_{12}H_{13}O_2N_1$ (M^+) 203.0941, found 203.0939.

4.2.3. *N*-(2-Formylphenyl)-*N*-methylcinnamamide ***(1c)***. Yellow solid, yield 76% (2.015 g), mp: 89-90 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.37 (3H, s, NCH_3), 6.05 (1H, d, *J* = 15.4 Hz), 7.16-7.33 (6H, m, Ar-H), 7.50 (1H, t, *J* = 7.4 Hz, Ar-H), 7.64 (1H, d, *J* = 15.4 Hz, =CH), 7.65 (1H, dt, *J* = 7.7, 1.5 Hz, Ar-H), 7.95 (1H, dd, *J* = 7.7, 1.5 Hz, Ar-H), 10.05 (1H, s, -CHO); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 38.5 (NCH_3), 117.5 (CH), 127.9 (CH), 128.7 (CH), 128. 9 (CH), 129.4 (CH), 129.7 (CH), 129.8 (CH), 132.8 (C), 134.6 (C), 135.6 (CH), 143.3 (CH), 145.5 (C), 166.3 (CON), 189.1 (CHO). IR (ATR, cm^{-1}): ῡ= 3061, 3031, 2930, 2850, 2748, 1685, 1656, 1622, 1593, 1419, 1361, 1251, 1089, 968, 821, 756, 699, 563. HRMS (ESI): calcd for $C_{17}H_{15}O_2N_1$ (M^+) 265.1097, found 265.1094.

4.2.4. *N*-Ethyl-*N*-(2-formylphenyl)acrylamide ***(1d)***. Light brown liquid, yield 78% (1.585 g). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.11 (3H, t, *J* = 7.2 Hz, CH_3), 3.61-4.05 (2H, m, NCH_2-), 5.46 (1H, dd, *J* = 10.3, 1.9 Hz), 5.76 (1H, dd, *J* = 16.7, 10.3 Hz), 6.33 (1H, dd, *J* = 16.7, 1.9 Hz), 7.21 (1H, dd, *J* = 7.8, 0.9 Hz, Ar-H), 7.48 (1H, t, *J* = 7.6, Ar-H), 7.64 (1H, dt, *J* = 7.6, 1.7 Hz, Ar-H), 7.94 (1H, dd, *J* = 7.7, 1.6 Hz, Ar-H), 10.02 (1H, s, -CHO); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 12.6 (CH_3), 45.3 (NCH_2), 128.0 (CH), 128.8 (CH), 129.0 (CH_2), 129.5 (CH), 130.0 (CH), 133.3 (C), 135.3 (CH), 143.8 (C), 165.3 (CON), 189.4 (CHO). IR (ATR, cm^{-1}): ῡ= 2972, 2933, 2873, 2750, 1693, 1655, 1593, 1407, 1259, 1188, 979, 769. HRMS (ESI): calcd for $C_{12}H_{13}O_2N_1$ (M^+) 203.0941, found 203.0939.

4.2.5. (*E*)-*N*-Ethyl-*N*-(2-formylphenyl)but-2-enamide ***(1e)***. Light brown liquid, yield 73% (1.585 g). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.09 (3H, t, *J* = 7.1 Hz, CH_3), 1.62 (3H, dd, *J* = 6.9, 1.4 Hz, CH_3), 3.59-4.02 (2H, m, NCH_2-), 5.42 (1H, dq, *J* = 15.0, 1.4 Hz), 6.80-6.98 (1H, m), 7.18-7.22 (1H, m, Ar-H), 7.47 (1H, t,

J = 7.5 Hz, Ar-H), 7.64 (1H, td, *J* = 7.7, 1.4 Hz, Ar-H), 7.94 (1H, dd, *J* = 7.7, 1.3 Hz, Ar-H), 10.01 (1H, s, -CHO); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 11.7 (CH_3), 17.0 (CH_3), 44.2 (NCH_2), 121.3 (CH), 127.7 (CH), 128.2 (CH), 129.1 (CH), 132.4 (C), 134.4 (CH), 142.1 (CH), 143.3 (C), 164.7 (CON), 188.6 (CHO). IR (ATR, cm^{-1}): ϑ= 3072, 2979, 2929, 2870, 2855, 2754, 1682, 1661, 1623, 1593, 1445, 1393, 1375, 1246, 1135, 1094, 974, 824, 772, 575. HRMS (ESI): calcd for $C_{13}H_{15}O_2N_1$ (M^+) 217.1097, found 217.1097.

4.2.6. *N*-Ethyl-*N*-(2-formylphenyl)cinnamamide ***(1f)***. Yellow solid, yield 65% (1.815 g), mp: 60-62 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.20 (3H, t, *J* = 7.2 Hz, CH_3), 3.69-4.19 (2H, m, NCH_2-), 6.07 (1H, d, *J* = 15.4 Hz), 7.22-7.33 (6H, m, Ar-H), 7.57 (1H, t, *J* = 7.6 Hz, Ar-H), 7.68-7.76 (2H, m, Ar-H & =CH-), 8.04 (1H, dd, *J* = 7.7, 1.6 Hz, Ar-H), 10.14 (1H, s, -CHO); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 12.7 (CH_3), 45.5 (NCH_2), 117.9 (CH), 127.9 (CH), 128.6 (CH), 128.8 (CH), 129.4 (CH), 129.8 (CH), 130.2 (CH), 133.4 (C), 134.7 (C), 135.3 (CH), 143.3 (CH), 144.1 (C), 165.8 (CON), 189.4 (CHO). IR (ATR, cm^{-1}): ϑ= 3062, 3028, 2974, 2932, 2850, 2752, 1689, 1653, 1616, 1592, 1372, 1233, 971, 759. HRMS (ESI): calcd for $C_{18}H_{17}O_2N_1$ (M^+) 279.1254, found 279.1253.

4.3. General procedure for domino Knoevenagel-hetero-Diels–Alder reaction

To a stirred solution of *N*-acrylated anthranilaldehyde **1** (0.5 mmol) and indolin-2-thione **2** (0.5 mmol) in EtOH (7 ml) was added $ZnBr_2$ (20 mol%), Then the reaction mixture was stirred at reflux. The progress of the reaction was monitored by TLC. After completion of the reaction (3 h), which is with precipitation of the product, the mixture was poured onto ice-cold water (20 ml) and stirred for 5 min., the precipitate was filtered and washed with water, after drying, recrystallized from ethanol to produce pure product **3**.

4.3.1. *(6aS*,13cR*)-5,9-Dimethyl-6a,7,9,13c-tetrahydroindolo[3',2':5,6] thiopyrano[3,4-c]quinolin-6(5H)-one (**3a**)*. Pale yellow powder, yield 90% (150 mg), mp: 223-225 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.06-3.27 (3H, m, Ha & Hb), 3.44 (3H, s, NCH_3), 3.64 (3H, s, NCH_3), 4.69 (1H, d, *J* = 4.0 Hz,

Hc), 6.84-7.23 (6H, m, Ar-H), 7.27-7.40 (2H, m, Ar-H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 24.5 (CH_2), 29.9 (NCH_3), 30.0 (NCH_3), 33.0 (CH), 41.9 (CH), 103.4 (C), 108.3 (CH), 114.7 (CH), 116.7 (CH), 119.7 (CH), 120.6 (CH), 123.5 (CH), 127.7 (CH), 128.2 (C), 128.7 (C), 129.3 (CH), 129.4 (C), 137.3 (C), 138.3 (C), 170.7 (CO). IR (ATR, cm^{-1}): ϑ= 2930, 1664, 1603, 1468, 1374, 1278, 1120, 756. HRMS (ESI): calcd for $C_{20}H_{18}N_2O_1S_1$ (M^+) 334.1134, found 334.1131.

4.3.2. *(6aS*,7S*,13cR*)-5,7,9-Trimethyl-6a,7,9,13c-tetrahydroindolo[3',2':5,6] thiopyrano[3,4-c]quinolin-6(5H)-one (**3b**).* Pale yellow powder, yield 88% (154 mg), mp: 238-240 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.46 (3H, d, *J* = 6.8 Hz, CH_3), 2.99 (1H, dd, *J* = 9.6, 4.6 Hz, Hb), 3.44 (3H, s, NCH_3), 3.48-3.59 (1H, m, Ha), 3.63 (3H, s, NCH_3), 4.71 (1H, d, *J* = 4.5 Hz, Hc), 6.92-7.24 (6H, m, Ar-H), 7.29-7.35 (2H, m, Ar-H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 19.3 (CH_3), 29.8 (CH_3), 29.9 (CH_3), 33.2 (CH), 33.8 (CH), 48.4 (CH), 103.1 (C), 108.3 (CH), 114.9 (CH), 116.7 (CH), 119.6 (CH), 120.4 (CH), 123.4 (CH), 127.8 (CH), 128.4 (C), 128.9 (C), 129.1 (CH), 130.4 (C), 137.3 (C), 138.4 (C), 169.3 (CO). IR (ATR, cm^{-1}): ϑ= 3053, 2924, 1670, 1596, 1498, 1451, 1367, 751, 698. HRMS (ESI): calcd for $C_{21}H_{20}N_2O_1S_1$ (M+H) 349.1369, found 349.1367.

4.3.3. *(6aS*,7R*,13cR*)-5,9-Dimethyl-7-phenyl-6a,7,9,13c-tetrahydroindolo [3',2':5,6]thiopyrano[3,4-c]quinolin-6(5H)-one (**3c**).* Light brown powder, yield 95% (195 mg), mp: 185-186 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.19 (3H, s, NCH_3), 3.32 (1H, dd, *J* = 8.2, 4.5 Hz, Hb), 3.58 (3H, s, NCH_3), 4.54 (1H, d, *J* = 3.8 Hz, Hc), 4.67 (1H, d, *J* = 8.5 Hz, Ha), 6.88-7.24 (11H, m, Ar-H), 7.28-7.34 (2H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.9 (NCH_3), 33.7 (NCH_3), 43.5 (CH), 48.1 (CH), 49.0 (CH), 103.2 (C), 108.3 (CH), 109.6 (C), 114.9 (CH), 117.1 (CH), 119.6 (CH), 120.5 (CH), 123.3 (CH), 128.0 (C), 128.1 (CH), 128.3 (C), 128.4 (CH), 128.5 (CH), 128.6 (CH), 129.5 (CH), 130.5 (C), 137.3 (C), 138.8 (C), 168.5 (CO). IR (ATR, cm^{-1}): ϑ= 3047, 2914, 1666, 1598, 1462, 1355, 1088, 753. HRMS (ESI): calcd for $C_{26}H_{22}N_2O_1S_1$ (M^+) 410.1447, found 410.1439.

4.3.4. *(6aS*,13cR*)-5-Ethyl-9-methyl-6a,7,9,13c-tetrahydroindolo[3',2':5,6] thiopyrano[3,4-c]quinolin-6(5H)-one (**3d**).* Pale white powder, yield 87% (151 mg), mp: 200-201 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.31 (3H, t, *J* = 7.1 Hz,

CH_3), 3.05-3.19 (3H, m, Ha & Hb), 3.64 (3H, s, NCH_3), 4.07 (2H, dq, *J* = 7.1, 2.5 Hz, NCH_2-), 4.67 (1H, d, *J* = 3.1 Hz, Hc), 6.90-7.38 (8H, m, Ar-H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 12.8 (CH_3), 24.3 (CH_2), 29.9 (NCH_3), 33.0 (CH), 37.6 (NCH_2) , 41.9 (CH), 103.5 (C), 108.3 (CH), 114.7 (CH), 116.7 (CH), 119.7 (CH), 120.6 (CH), 123.5 (CH), 127.7 (CH), 128.5 (C), 128.7 (C), 129.3 (C), 129.6 (CH), 137.1 (C), 137.3 (C), 170.1 (CO). IR (ATR, cm^{-1}): ῡ= 3045, 2929, 1663, 1596, 1461, 1379, 750, 729. HRMS (ESI): calcd for $C_{21}H_{20}N_2O_1S_1$ (M^+) 348.1291, found 348.1284.

4.3.5. *(6aS*,7S*,13cR*)-5-Ethyl-7,9-dimethyl-6a,7,9,13c-tetrahydroindolo [3',2':5,6]thiopyrano[3,4-c]quinolin-6(5H)-one (**3e**).* Cream powder, yield 83% (150 mg), mp: 165-167 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.32 (3H, t, *J* = 7.1 Hz, CH_3), 1.45 (3H, d, *J* = 6.9 Hz, CH_3), 2.95 (1H, dd, *J* = 10.0, 4.5 Hz, Hb), 3.49-3.55 (1H, m, Ha), 3.63 (3H, s, NCH_3), 3.85-4.27 (2H, m, NCH_2-), 4.71 (1H, d, *J* = 4.5 Hz, Hc), 6.88-7.25 (5H, m, Ar-H), 7.27-7.37 (3H, m, Ar-H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 13.0 (CH_3), 19.0 (CH_3), 29.9 (NCH_3), 33.1 (CH), 33.9 (CH), 38.0 (NCH_2), 48.6 (CH), 103.4 (C), 108.3 (CH), 114.7 (CH), 116.7 (CH), 119.6 (CH), 120.4 (CH), 123.3 (CH), 127.7 (CH), 128.5 (C), 129.2 (C), 129.3 (CH), 130.4 (C), 137.30 (C), 137.34 (C), 168.8 (CO). IR (ATR, cm^{-1}): ῡ= 2926, 1662, 1597, 1492, 1457, 1370, 1312, 1248, 748, 737. HRMS (ESI): calcd for $C_{22}H_{22}N_2O_1S_1$ (M^+) 362.1447, found 362.1441.

4.3.6. *(6aS*,7R*,13cR*)-5-Ethyl-9-methyl-7-phenyl-6a,7,9,13c-tetrahydroindolo[3',2':5,6]thiopyrano[3,4-c]quinolin-6(5H)-one (**3f**).* Yellow powder, yield 92% (195 mg), mp: 139-140 ºC. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.99 (3H, t, *J* = 7.1 Hz, CH_3), 3.31 (1H, dd, *J* = 9.4, 4.4 Hz, Hb), 3.58 (3H, s, NCH_3), 3.50-4.05 (2H, m, NCH_2), 4.56-4.59 (2H, m, Ha & Hc), 6.90 (1H, dt, *J* = 7.5, 0.9 Hz, Ar-H), 7.00 (2H, t, *J* = 6.9 Hz, Ar-H), 7.06-7.13 (2H, m, Ar-H), 7.18-7.30 (8H, m, Ar-H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 12.8 (CH_3), 29.9 (NCH_3), 34.0 (CH), 38.2 (NCH_2), 43.5 (CH), 48.2 (CH), 103.4 (C), 108.4 (CH), 114.5 (C), 114.7 (CH), 116.9 (CH), 119.7 (CH), 120.5 (CH), 123.2 (CH), 128.0 (CH), 128.4 (C), 128.5 (CH), 128.6 (CH), 128.8 (CH), 128.9 (C), 129.7 (CH), 130.6 (C), 137.3 (C), 137.8 (C), 167.8 (CO). IR (ATR, cm^{-1}): ῡ= 3047, 2929, 1667, 1595, 1454, 1355, 1312, 1088, 747. HRMS (ESI): calcd for $C_{27}H_{24}N_2O_1S_1$ (M^+) 424.1604, found 424.1592.

4.3.7. *(6aS*,13cR*)-9-Ethyl-5-methyl-6a,7,9,13c-tetrahydroindolo[3',2':5,6] thiopyrano[3,4-c]quinolin-6(5H)-one (**3g**).* Cream powder, yield 90% (157 mg), mp: 189-190 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* = 7.2 Hz, CH_3), 2.97-3.20 (3H, m, Ha & Hb), 3.37 (3H, s, NCH_3), 3.95-4.10 (2H, m, NCH_2-), 4.63 (1H, d, *J* = 4.4 Hz, Hc), 6.85-7.35 (8H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.9 (CH_3), 24.4 (CH_2), 30.0 (NCH_3), 33.0 (CH), 38.7 (NCH_2), 42.0 (CH), 103.4 (C), 108.4 (CH), 114.7 (CH), 116.8 (CH), 119.6 (CH), 120.5 (CH), 123.6 (CH), 127.7 (CH), 128.2 (C), 128.4 (C), 128.9 (C), 129.3 (CH), 136.2 (C), 138.3 (C), 170.8 (CO). IR (ATR, cm^{-1}): ϋ= 3045, 2971, 2930, 1656, 1596, 1461, 1443, 1375, 1119, 755, 726. HRMS (ESI): calcd for $C_{21}H_{20}N_2O_1S_1$ (M^+) 348.1291, found 348.1285.

4.3.8. *(6aS*,13cR*)-5-Methyl-9-phenyl-6a,7,9,13c-tetrahydroindolo[3',2':5,6] thiopyrano[3,4-c]quinolin-6(5H)-one (**3h**).* Pale white powder, yield 85% (168 mg), mp: 135-136 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98-3.14 (2H, m, Ha), 3.25-3.31 (1H, m, Hb), 3.46 (3H, s, NCH_3), 4.77 (1H, d, *J* = 4.7 Hz, Hc), 6.97-7.23 (5H, m, Ar-H), 7.29-7.56 (8H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7 (CH_2), 30.0 (NCH_3), 33.1 (CH), 42.0 (CH), 105.2 (C), 109.6 (CH), 114.8 (CH), 116.8 (CH), 117.0 (C), 120.5 (C), 121.3 (CH), 123.6 (CH), 127.2 (CH), 127.7 (CH), 127.8 (CH), 127.9 (C), 128.1 (CH), 129.2 (C), 129.3 (CH), 129.6 (CH), 129.7 (C), 138.3 (C), 170.7 (CO). IR (ATR, cm^{-1}): ϋ= 3049, 2925, 1661, 1595, 1497, 1449, 1363, 740, 697. HRMS (ESI): calcd for $C_{25}H_{20}N_2O_1S_1$ (M^+) 396.1291, found 396.1287.

4.3.9. *(6aS*,7S*,13cR*)-5,7-Dimethyl-9-phenyl-6a,7,9,13c-tetrahydroindolo [3',2':5,6]thiopyrano[3,4-c]quinolin-6(5H)-one (**3i**).* Cream powder, yield 90% (185 mg), mp: 153-154 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (3H, d, *J* = 6.8 Hz, CH_3), 3.05 (1H, dd, *J* = 10.0, 4.6 Hz, Hb), 3.42-3.54 (4H, m, NCH_3 & Ha), 4.81 (1H, d, *J* = 4.4 Hz, Hc), 6.96-7.25 (6H, m, Ar-H), 7.27-7.56 (7H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.0 (CH_3), 30.1 (NCH_3), 33.3 (CH), 34.0 (CH), 48.6 (CH), 105.1 (C), 109.7 (CH), 114.9 (CH), 116.8 (CH), 120.5 (CH), 121.2 (CH), 123.5 (CH), 127.2 (CH), 127.8 (CH), 128.1 (CH), 128.7 (C), 128.9 (C), 129.1 (CH), 129.5 (CH), 130.7 (C), 136.7 (C), 137.8 (C), 138.4 (C), 169.4 (CO). IR (ATR, cm^{-1}): ϋ= 3053, 2927, 1668, 1597, 1490, 1454, 1367, 749. HRMS (ESI): calcd for $C_{26}H_{22}N_2O_1S_1$ (M^+) 410.1447, found 410.1444.

4.3.10. *(6aS*,7R*,13cR*)-5-Methyl-7,9-diphenyl-6a,7,9,13c-tetrahydroindolo [3',2':5,6]thiopyrano[3,4-c]quinolin-6(5H)-one (**3j**).* Cream powder, yield 94% (223 mg), mp: 255-256 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30 (3H, s, NCH_3), 3.52 (1H, dd, *J* = 9.3, 4.4 Hz, Hb), 4.64 (1H, d, *J* = 9.3 Hz, Ha), 4.79 (1H, d, *J* = 3.7 Hz, Hc), 7.05-7.30 (5H, m, Ar-H), 7.35-7.57 (13H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.9 (NCH_3), 34.1 (CH), 43.8 (CH), 48.3 (CH), 105.1 (C), 109.7 (CH), 114.9 (CH), 117.1 (CH), 120.5 (CH), 121.3 (CH), 123.4 (CH), 127.2 (CH), 128.12 (CH), 128.14 (CH), 128.4 (C), 128.5 (CH), 128.6 (CH), 128.9 (CH), 129.5 (CH), 129.6 (CH), 130.9 (C), 136.6 (C), 137.4 (C), 137.5 (C), 137.7 (C), 138.7 (C), 168.4 (CO). IR (ATR, cm^{-1}): ῡ= 3061, 2937, 1670, 1595, 1497, 1365, 762, 750, 696. HRMS (ESI): calcd for $C_{31}H_{24}N_2O_1S_1$ (M+H) 473.1682, found 473.1677.

4.3.11. *(6aS*,13cR*)-5-Ethyl-9-phenyl-6a,7,9,13c-tetrahydroindolo[3',2':5,6] thiopyrano[3,4-c]quinolin-6(5H)-one (**3k**).* Light brown powder, yield 87% (178 mg), mp: 135-136 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (3H, t, *J* = 7.0 Hz, CH_3), 2.98-3.15 (2H, m, Ha), 3.22-3.28 (1H, m, Hb), 4.02-4.16 (2H, m, NCH_2-), 4.74 (1H, d, *J* = 4.2 Hz, Hc), 6.96-7.22 (5H, m, Ar-H), 7.28-7.58 (8H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.8 (CH_3), 24.5 (CH_2), 33.1 (CH), 37.7 (NCH_2), 42.0 (CH), 105.4 (C), 109.6 (CH), 114.8 (CH), 116.8 (CH), 120.5 (CH), 121.3 (CH), 123.5 (CH), 127.2 (CH), 127.8 (CH), 127.9 (C), 128.1 (CH), 129.2 (C), 129.4 (C), 129.5 (CH), 129.6 (CH), 136.7 (C), 137.2 (C), 137.7 (C), 170.2 (CO). IR (ATR, cm^{-1}): ῡ= 3044, 2964, 2928, 1663, 1593, 1496, 1447, 739, 694. HRMS (ESI): calcd for $C_{26}H_{22}N_2O_1S_1$ (M^+) 410.1447, found 410.1436.

Supplementary data

^{1}H NMR, ^{13}C NMR and DEPT 135 spectra of compounds **1a-f** and **3a-k** are submitted in separated file as supplementary data.

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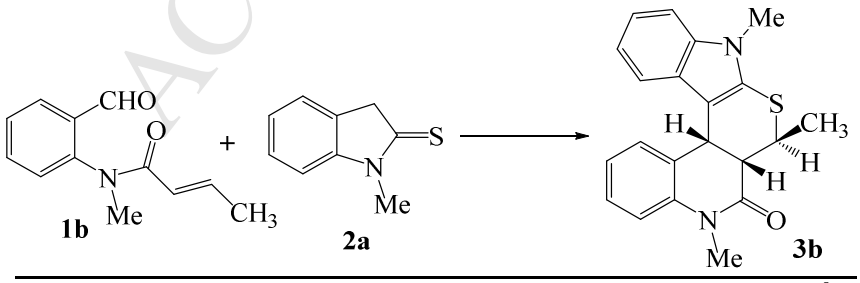
Table 1
Effect of catalysts and solvents on the domino Knoevenagel-hetero-Diels–Alder reaction of compounds **1b** and **2a**



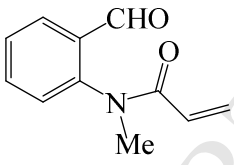
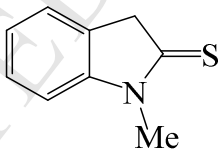
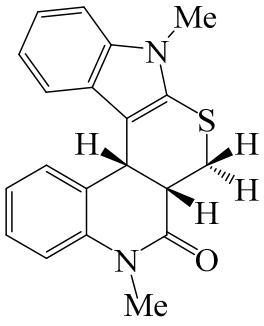
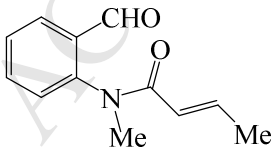
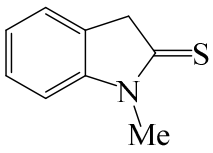
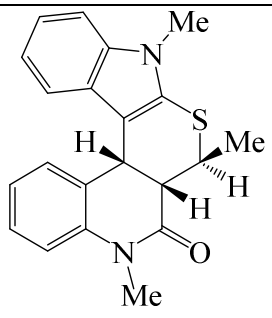
Entry	Solvent	Catalyst	Temp. (°C)	Time (h)	Yield[a] (%)

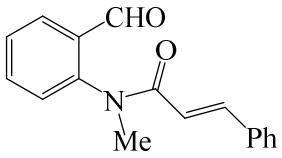
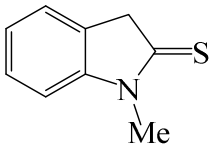
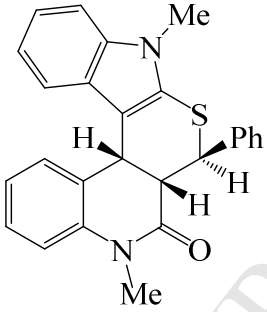
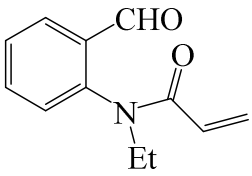
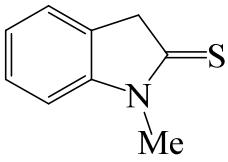
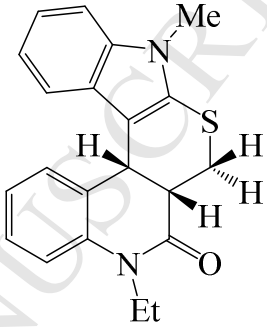
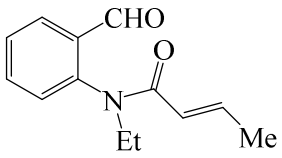
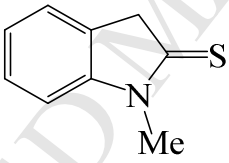
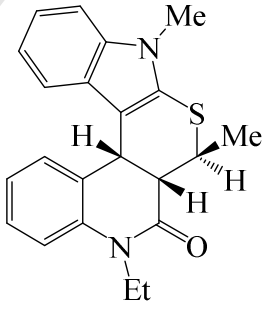
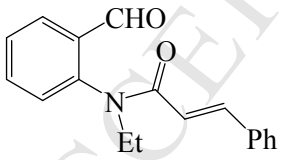
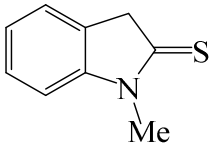
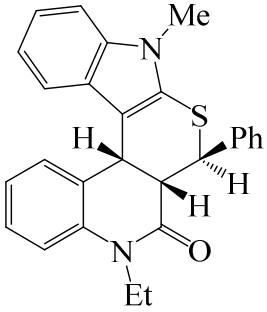
1	H_2O	-	Reflux	24	10
2	CH_3CN	-	Reflux	24	12
3	CH_3CN	ZnO (100%)	Reflux	24	35
4	MeOH	ZnO (100%)	Reflux	24	30
5	EtOH	ZnO (100%)	Reflux	24	48
6	EtOH	$ZnBr_2$ (100%)	Reflux	3	88
7	EtOH	$ZnBr_2$ (50%)	Reflux	3	88
8	EtOH	$ZnBr_2$ (20%)	Reflux	3	88
9	EtOH	$ZnBr_2$ (10%)	Reflux	3	68
10	EtOH	Et_3N	Reflux	24	0
11	EtOH	$ZnCl_2$ (20%)	Reflux	24	60
12	H_2O	$ZnBr_2$ (20%)	Reflux	24	22

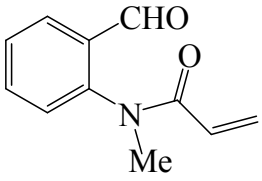
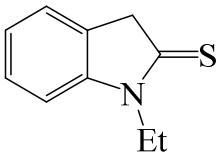
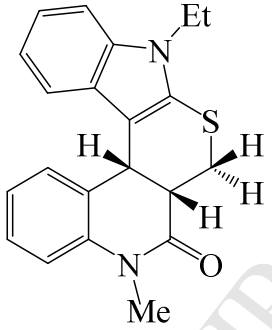
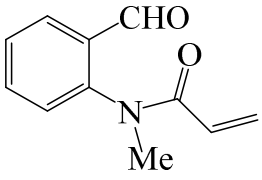
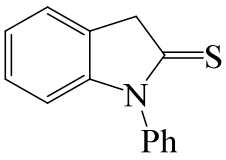
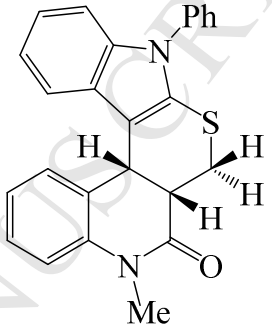
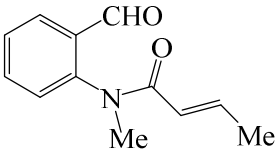
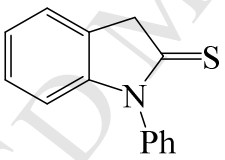
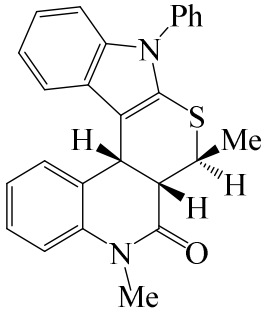
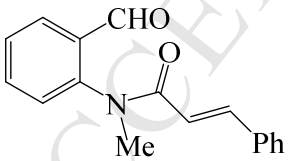
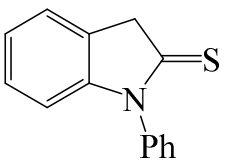
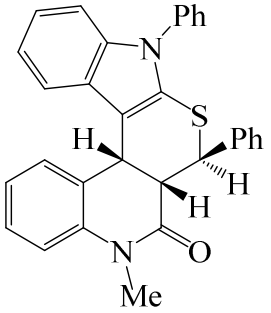
[a] Yield of isolated products.

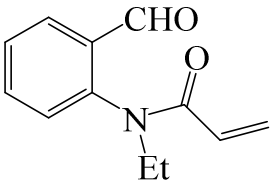
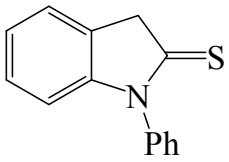
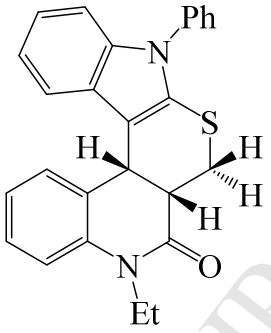
Table 2

Domino Knoevenagel-hetero-Diels–Alder reactions of *N*-acrylated anthranilaldehyde derivatives **1a-f** with indoline-2-thiones **2a-c**[a]

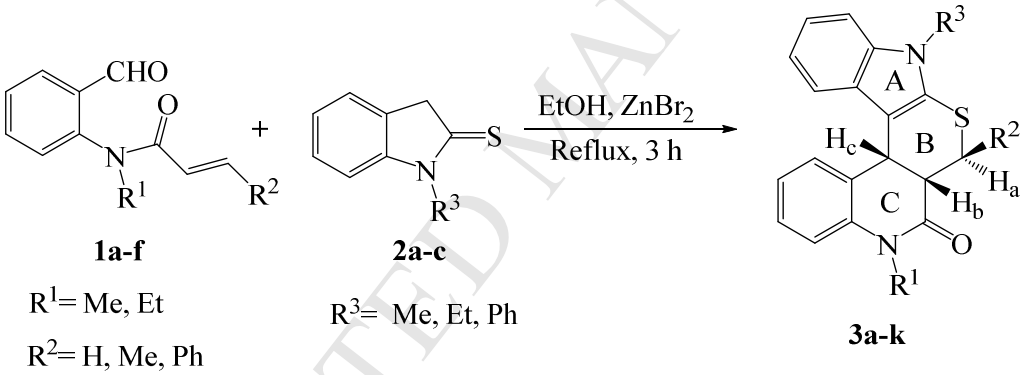
Entry	Aldehydes **1**	Indoline-2-thiones **2**	Products **3**	Yield[b]
1	 **1a**	 **2a**	 **3a**	90
2	 **1b**	 **2a**	 **3b**	88

3	 **1c**	 **2a**	 **3c**	95
4	 **1d**	 **2a**	 **3d**	87
5	 **1e**	 **2a**	 **3e**	83
6	 **1f**	 **2a**	 **3f**	92

7	 **1a**	 **2b**	 **3g**	90
8	 **1a**	 **2c**	 **3h**	85
9	 **1b**	 **2c**	 **3i**	90
10	 **1c**	 **2c**	 **3j**	94

11	 **1d**	 **2c**	 **3k**	87

[a] All the reactions were carried out at reflux in the EtOH for 3 h in the presence of $ZnBr_2$ (20 mol%).
[b] Isolated products.



1a-f

R^1= Me, Et

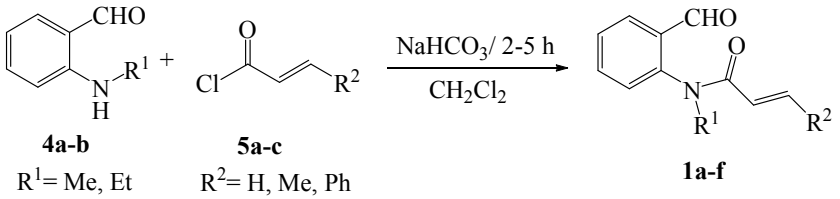
R^2= H, Me, Ph

2a-c

R^3= Me, Et, Ph

3a-k

Scheme 1.



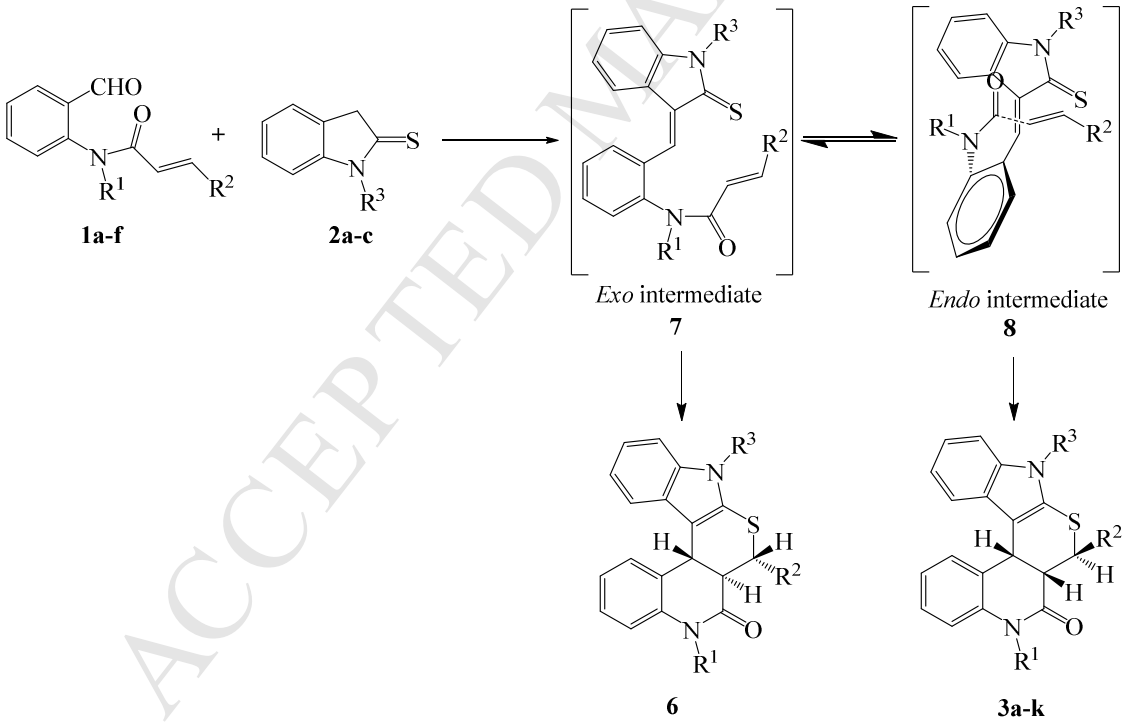
4a-b
R^1= Me, Et

5a-c
R^2= H, Me, Ph

1a-f

	R^1	R^2	Yield (%)
1a	Me	H	85
1b	Me	Me	80
1c	Me	Ph	76
1d	Et	H	78
1e	Et	Me	73
1f	Et	Ph	65

Scheme 2.



1a-f **2a-c**

Exo intermediate
7

Endo intermediate
8

6 **3a-k**

Scheme 3. A plausible mechanism for the formation of compounds **3a-k**.