A multicomponent reaction as a versatile tool for the synthesis of spirooxindoles using *N*-alkylisatins; efficient catalysis by ZnO nanoparticles

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An efficient and green protocol for the synthesis of functionalised spirooxindole derivatives is described. This involves the reaction of *in situ*-generated keto-enaminones with *N*-alkylisatins in the presence of isothiocyanates.

Keywords: oxindole derivatives, 1,3-dicarbonyl compounds, three-component reaction, isothiocyanates, *N*-alkylisatin

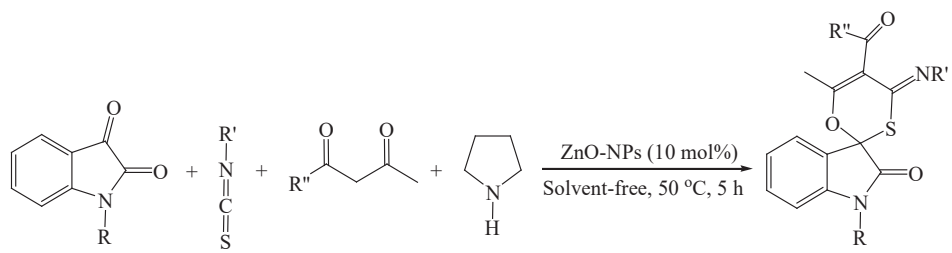
Isatin is an endogenous compound identified in humans that has a wide range of biological activities. Isatin has antiogenic, sedative and anticonvulsant activities and acts as a potent antagonist on atrial natriuretic peptide receptors *in vitro*.[1] A range of substituted *N*-alkylisatins have been synthesised and their cytotoxicity evaluated against several cancer cell lines *in vitro*. Structure–activity relationship studies have indicated that the introduction of an aromatic ring with a one or three carbon atom linker at N1 enhances the activity.[2] Multicomponent reactions (MCRs) are important in medicinal and pharmaceutical chemistry[3–6] and are one of the best procedures for the synthesis of heterocyclic compounds with biological activity and high molecular complexity.[7–10] The spirooxindole system is the core structure of a variety of medicinal agents and natural products.[11,12] In fact, spirooxindole derivatives have been described with different biological activities, ranging from anti-tumour, anti-microbial, anti-HIV and antipyretic agents to sodium channel blockers and antimalarials.[13–15] Compared with the usual stepwise approaches, MCRs are notable because of their ability to provide powerful synthetic processes with advantages in terms of time, cost and waste minimisation.[16–22] Both academic and industrial groups utilise MCRs because of their great versatility to find potent biologically active compounds for various applications.[23–27] Also, in recent years, green chemistry has become very important.[28–29] The chief aims of green chemistry are the expansion of cleaner and more benign chemical processes by replacement of volatile and dangerous reagents and solvents with environmentally compatible compounds, therefore increasing process selectivity.[30–37]

Results and discussion

In this paper, we show an efficient synthesis of oxindole derivatives in 85–95% yield *via* the reaction of *N*-alkylisatins **1**, isothiocyanates **2**, 1,3-dicarbonyl compounds **3** and pyrrolidine **4** in the presence of ZnO nanoparticles (ZnO-NPs)[38–40] under solvent-free conditions at 50 °C (Scheme 1).

The starting step for our experiments was to optimise the reaction conditions, such as solvent, catalyst and reaction time, for the generation of spirooxindole derivatives (Table 1). The results indicated that simple mixing of an *N*-alkylisatin **1** (2 mmol), an isothiocyanate **2** (2 mmol) and an enamine produced by the reaction of a 1,3-dicarbonyl compound **3** and pyrrolidine **4**, is an efficient method for preparation of spirooxindole derivatives **5** in good yields.

In the optimised reaction conditions, the temperature of the reaction mixture is 50 °C and the reaction was performed under solvent-free conditions in the presence of ZnO-NPs. The ZnO nanostructure was prepared according to the literature procedure.[38] Under these conditions, oxindole derivatives **5** were produced in good yield. In these reactions, some alternative catalysts, such as ZnO nanorods (ZnO-NR), ZnO nanosheets (ZnO-NS), commercial ZnO (CM-ZnO), TiO_2-NPs, CuO-NPs and KF/clinoptilolite NPs (KF/CP NPs), were also used. Amongst these catalysts, ZnO-NPs were the best for these



1 **2** **3** **4** **5**

1, 2, 3, 5	R	R'	R''	Yield of 5/%
a	Me	4-$MeOC_6H_4$	Me	92
b	Me	4-MeC_6H_4	OEt	85
c	Et	4-$O_2NC_6H_4$	Me	87
d	Bn	4-$MeOC_6H_4$	Me	90
e	Bn	^{t}Bu	Me	92
f	Me	^{t}Bu	OEt	93
g	Et	^{t}Bu	Me	95
h	Bn	4-BrC_6H_4	Me	85

Scheme 1 Reaction of *N*-alkylisatins, isothiocyanates, 1,3-dicarbonyl compounds and pyrrolidine in the presence of ZnO nanoparticles.

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Table 1 Optimisation of reaction conditions of compound **5a**

Entry	Solvent[a]	Catalyst	T/°C	Time/h	Yield/%[b]
1	DMF	–	90	10	15
2	Toluene	ZnO-NPs	50	8	56
3	Toluene	ZnO-NPs	90	8	57
4	CH_3CN	ZnO-NPs	80	10	40
5	CH_3CN	ZnO-NPs	50	10	40
6	EtOH	ZnO-NPs	80	12	10
7	EtOH	ZnO-NPs	90	12	10
8	H_2O	–	r.t.	6	–
9	H_2O	ZnO-NPs	r.t.	6	10
10	H_2O	ZnO-NPs	50	6	25
11	H_2O	ZnO-NPs	80	6	25
12	Solvent-free	–	r.t.	5	5
13	Solvent-free	ZnO-NPs	r.t.	5	80
14	Solvent-free	ZnO-NPs	50	5	92
15	Solvent-free	ZnO-NPs	70	5	92
16	Solvent-free	ZnO-NR	50	12	75
17	Solvent-free	ZnO-NS	50	10	68
18	Solvent-free	TiO_2-NPs	50	10	35
19	Solvent-free	CuO-NPs	50	10	47
20	Solvent-free	KF/CP NPs	50	8	78
21	Solvent-free	$ZnCl_2$	50	12	65
22	Solvent-free	ZnI_2	50	12	38
23	EtOH	$ZnCl_2$	50	12	28
24	H_2O	$ZnCl_2$	50	12	–
25	Solvent-free	CM-ZnO	–	15	37
26	Solvent-free	CM-ZnO	50	12	45

[a]The amount of solvent was 5 mL.

[b]Isolated yield for reaction under solvent-free conditions

reactions. The amount of catalyst is 10 mol%. Using a catalyst loading of more than 10 mol% decreased the yield of product.

It was found that ZnO-NPs can be reused five times without significant loss of activity. The catalyst was filtered off after each run and washed completely with ethyl acetate. It was then dried at room temperature for 24 h and employed for the next catalytic cycle.

The structures of compounds **5a**–**h** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, the ^{1}H NMR spectrum of **5a** displayed two singlets for the methyl protons at δ 2.23 and 2.28 ppm, one singlet at δ 3.32 for the NMe protons and a singlet for the methoxy protons at 3.78 ppm along with signals from the aromatic moiety. The ^{13}C NMR spectrum of **5a** showed a signal for the spiro carbon at 91.6 ppm and two signals for the carbonyl groups at 164.6 and 192.4 ppm in agreement with the proposed structure. Moreover the mass spectra of **5a** exhibited the molecular ion peak at the appropriate *m*/*z* value.

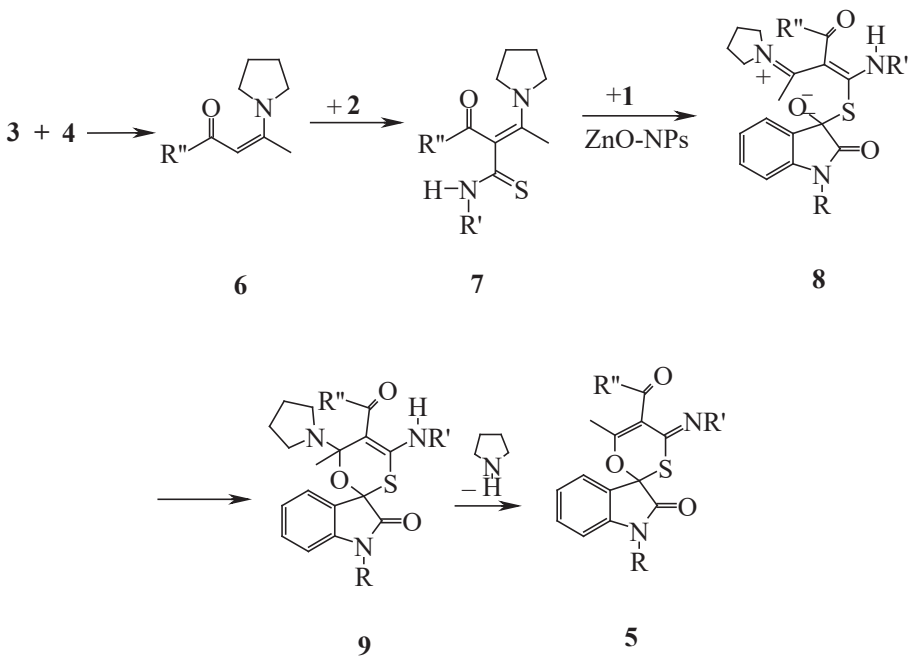
Mechanistically, it is possible that the reaction involves the initial formation of enaminone **6** from the reaction of 1,3-dicarbonyl compounds **3** and pyrrolidine **4** (Scheme 1). The enaminone **6**, as a nucleophile, subsequently reacts with isothiocyanate **2** in the presence of ZnO-NPs to produce enaminone **7**.[41,42] After that, nucleophilic attack of **7** on the carbonyl group of *N*-alkylisatin **1** leads to the zwitterionic species **8**. Finally, intramolecular cyclisation of **8** generates intermediate **9** which, following elimination of pyrrolidine, is converted to product **5**.

For confirmation of the mechanism of the reaction, one derivative of 7 was isolated and then reacted with an *N*-alkylisatin in the presence of ZnO-NPs (Scheme 3). After separation of compound **7a** and subsequent reaction with *N*-methylisatin **1a**, product **5a** was generated.

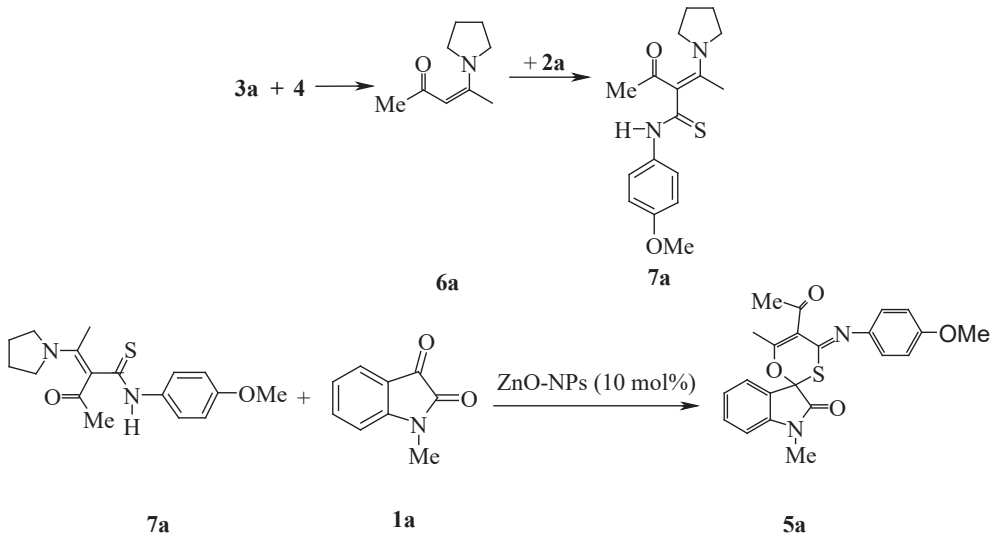
In this study, the reaction of isothiocyanates with *N*-alkylisatins and enaminones in the presence of a catalytic amount of ZnO-NPs at 50 °C under solvent-free conditions has been investigated and shown to provide a facile synthesis of some functionalised spirooxindoles.

Experimental

All chemicals used in this work were prepared by Fluka (Buchs, Switzerland) and were used without further purification. *N*-alkylisatins were synthesised using a literature procedure.[43] An Electrothermal 9100 apparatus was employed for measurement of melting points. Elemental analyses for C, H and N were performed with Heraeus CHN–O-Rapid analyser. Mass spectra were recorded on a Finnigan-MAT 8430 spectrometer operating at an ionisation potential of 70 eV.



Scheme 2 Proposed mechanism for the formation of **5**.



Scheme 3 Confirmation of the reaction mechanism for the formation of **5**.

Measurement of IR spectra was performed using a Shimadzu IR-460 spectrophotometer. ^{1}H and ^{13}C NMR spectra were evaluated with a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H NMR and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$ using TMS as an internal standard.

Preparation of ZnO nanoparticles

ZnO-NPs were prepared according to the literature procedure.[37] To a stirred solution of sodium hydroxide (0.44 g) in distilled water (75 mL) at room temperature, zinc acetate dihydrate (0.6 g) was added and the solution was heated for 1.5 h at 80 °C. Then, the solution was cooled at room temperature and the precipitate was collected by filtration and washed with distilled water and ethanol (96%) several times. ZnO-NPs were air dried at room temperature for 24 h.

Preparation of compounds (**7a**) *and* (**5a**)

To a magnetically stirred of acetylacetone **3a** (0.50 g, 5 mmol), pyrrolidine **4** (0.35 g, 5 mmol) was added. After 30 min, 4-methoxyphenyl isothiocyanate **2a** (0.83 g, 5 mmol) was added under solvent-free conditions. After completion of the reaction (TLC, AcOEt:hexane 1:6), the reaction mixture was purified by column chromatography on silica gel (Merck 230–400 mesh) using *n*-hexane–EtOAc as the eluent to afford pure compound **7a**.

*2-Acetyl-*N^{1}*-(4-methoxyphenyl)-3-(1-pyrrolidinyl)-2-butenethioamide* (**7a**): Yellow oil; yield 0.75 g (95%); IR (KBr) (υ_{max} cm^{-1}): 1720, 1687, 1547, 1478, 1363, 1227; MS (EI) *m/z* (%): 318 (M^{+}, 10), 275 (76), 43 (100); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (3 H, s, CH_3), 2.15 (4 H, m, 2 × CH_2), 2.38 (3 H, s, CH_3), 3.52 (4 H, m, 2 × CH_2), 3.78 (3 H, s, MeO), 7.04 (2 H, d, *J* = 7.4 Hz, 2 × CH), 7.15 (2 H, d, *J* = 7.4 Hz, 2 × CH); ^{13}C NMR (125.7 MHz, $CDCl_3$); δ 14.2 (Me), 26.3 (2 CH_2), 27.2 (Me), 49.5 (2 CH_2), 55.6 (MeO), 103.6 (C), 115.6 (2 CH), 117.2 (2 CH), 143.6 (C), 155.6 (C), 161.4 (C), 176.3 (C=S), 189.6 (C=O). Anal. calcd for $C_{17}H_{22}N_2O_2S$ (318.44): C, 64.12; H, 6.96; N, 8.80; found: C, 64.26; H, 7.08; N, 8.93%.

To a magnetically stirred solution of 7**a** (0.64 g, 2 mmol), *N*-methylisatin **1a** (0.32 g, 2 mmol) and ZnO-NPs (10 mol%) were added at 50 °C under solvent-free conditions. After completion of the reaction (monitored by TLC), ethyl acetate (5 mL) was poured into the reaction mixture. The catalyst was removed by filtration. The solvent evaporated from the mixture and the residue was purified by column chromatography (hexane:EtOAc 5:1) to afford compound **5a**.

Preparation of compounds (**5a**–**h**)*; general procedure*

To a magnetically stirred mixture of the 1,3-dicarbonyl compound **3** (2 mmol) and pyrrolidine **4** (2 mmol), the appropriate isothiocyanate **2** (2 mmol) and ZnO-NPs (10 mol%) were added at 50 °C under solvent-free conditions. After 30 min, the *N*-alkylisatin (2 mmol) was added to the mixture. Then, the reaction mixture was stirred for 5 h at 50 °C under solvent-free conditions. After completion of the reaction (TLC), ethyl acetate (5 mL) was poured into the reaction mixture. The catalyst was removed by filtration. The solvent was evaporated and the residue was purified by column chromatography (hexane:EtOAc 5:1) to afford **5**.

*1-Methyl-1,3-dihydro-2*H*-indol-2-one-spiro-1-{4-[(4-methoxyphenyl)imino]-6-methyl-4*H*-1,3-oxathiin-5-yl}-1-ethanone* (**5a**): Yellow powder; m.p. 152–154 °C; yield 0.75 g (92%); IR (KBr) (υ_{max} cm^{-1}): 1738, 1725, 1695, 1578, 1465, 1385, 1298; MS (EI) *m/z* (%): 408 (M^{+}, 15), 365 (82), 43 (100); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.23 (3 H, s, CH_3), 2.28 (3 H, s, CH_3), 3.32 (3 H, s, NMe), 3.78 (3 H, s, MeO), 6.87 (2 H, d, *J* = 7.5 Hz, 2 × CH), 7.12 (1 H, t, *J* = 7.8 Hz, CH), 7.22 (2 H, d, *J* = 7.5 Hz, 2 × CH), 7.32 (1 H, d, *J* = 7.6 Hz, CH), 7.68 (1 H, t, *J* = 7.8 Hz, CH), 7.92 (1 H, d, *J* = 7.8 Hz, CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 28.2 (Me), 28.6 (NMe), 29.3 (Me), 55.7 (MeO), 91.6 (C), 115.3 (2 CH), 119.4 (CH), 123.6 (2 CH), 124.2 (CH), 125.7 (CH), 130.2 (C), 131.4 (C), 132.7 (CH), 144.2 (C), 150.2 (C), 156.8 (C=N), 157.6 (C), 164.6 (C=O), 166.2 (C), 192.4 (C=O). Anal. calcd for $C_{22}H_{20}N_2O_4S$ (408.47): C, 64.69; H, 4.94; N, 6.86; found: C, 64.78; H, 5.06; N, 6.95%.

*1-Methyl-1,3-dihydro-2*H*-indol-2-one-spiro-{ethyl-6-methyl-4-[(4-methylphenyl)imino]-6-methyl-4*H*-1,3-oxathiine}-5-carboxylate* (**5b**)*:* Yellow powder; m.p. 164–166 °C; yield 0.72 g (85%); IR (KBr) (υ_{max} cm^{-1}): 1740, 1728, 1697, 1583, 1467, 1392, 1285; MS (EI) *m/z* (%): 422 (M^{+}, 15), 349 (82), 73 (100); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (3 H, t, *J* = 7.4 Hz, CH_3), 2.34 (3 H, s, Me), 2.40 (3 H, s, CH_3), 3.43 (3 H, s, NMe), 4.22 (2 H, q, *J* = 7.4 Hz, CH_2O), 6.92 (2 H, d, *J* = 7.6 Hz, 2 × CH), 7.09 (1 H, t, *J* = 7.6 Hz, CH), 7.18 (1 H, d, *J* = 7.6 Hz, CH), 7.25 (2 H, d, *J* = 7.6 Hz, 2 × CH), 7.73 (1 H, t, *J* = 7.8 Hz, CH), 7.83 (1 H, d, *J* = 7.8 Hz, CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.2 (Me), 21.4 (Me), 21.8 (Me), 28.6 (NMe), 61.2 (CH_2O), 92.4 (C), 119.6 (CH), 120.6 (C), 122.3 (2 CH), 123.5 (CH), 125.8 (CH), 129.2 (2 CH), 131.8 (C), 132.6 (CH), 134.6 (C), 148.7 (C), 149.5 (C), 155.2 (C=N), 163.4 (C=O), 164.6 (C=O), 175.2 (C). Anal. calcd for $C_{23}H_{22}N_2O_4S$ (422.49): C, 65.38; H, 5.25; N, 6.63; found: C, 65.47; H, 5.36; N, 6.72%.

*1-Ethyl-1,3-dihydro-2*H*-indol-2-one-spiro-1-{4-[(4-nitrophenyl)imino]-6-methyl-4*H*-1,3-oxathiin-5-yl}-1-ethanone* (**5c**): Yellow powder; m.p. 178–180 °C; yield 0.76 g (87%); IR (KBr) (υ_{max} cm^{-1}): 1742, 1722, 1685, 1574, 1452, 1364, 1252; MS (EI) *m/z* (%): 437 (M^{+}, 20), 394 (68), 43 (100); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (3 H, t, *J* = 7.5 Hz, CH_3), 2.26 (3 H, s, Me), 2.34 (3 H, s, CH_3), 4.36 (2 H, q, *J* = 7.5 Hz, NCH_2), 6.95 (1 H, t, *J* = 7.8 Hz, CH), 7.28 (1 H, d, *J* = 7.6 Hz, CH), 7.34 (2 H, d, *J* = 7.8 Hz, 2 × CH), 7.62 (1 H, t,

J = 7.6 Hz, CH), 7.82 (1 H, d, *J* = 7.8 Hz, CH), 8.34 (2 H, d, *J* = 7.8 Hz, 2 × CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.6 (Me), 28.4 (Me), 28.8 (Me), 41.7 (NCH_2), 93.6 (C), 122.2 (CH), 123.6 (2 CH), 124.2 (CH), 126.3 (2 CH), 126.8 (CH), 130.2 (C), 131.8 (C), 132.6 (CH), 148.2 (C), 150.2 (C), 156.2 (C), 156.8 (C=N), 164.8 (C=O), 166.3 (C), 192.6 (C=O). Anal. calcd for $C_{22}H_{19}N_3O_5S$ (437.47): C, 60.40; H, 4.38; N, 9.61; found: C, 60.52; H, 4.49; N, 9.73%.

*1-Benzyl-1,3-dihydro-2*H-*indol-2-one-spiro-1-{4-[(4-methoxyphenyl)imino]-6-methyl-4H-1,3-oxathiin-5-yl}-1-ethanone* (**5d**): Yellow powder; m.p. 183–185 °C; yield 0.87 g (90%); IR (KBr) (υ_{max} cm^{-1}): 1745, 1727, 1687, 1575, 1457, 1376, 1268; MS (EI) *m/z* (%): 484 (M$^+$, 10), 441 (72), 43 (100); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.28 (3 H, s, Me), 2.35 (3 H, s, CH_3), 3.78 (3 H, s, MeO), 4.86 (2 H, s, NCH_2), 6.94 (2 H, d, *J* = 7.6 Hz, 2 × CH), 7.15 (1 H, t, *J* = 7.8 Hz, CH), 7.23 (2 H, d, *J* = 7.6 Hz, 2 × CH), 7.23 (1 H, d, *J* = 7.8 Hz, CH), 7.26–7.38 (5 H, m, 5 × CH), 7.68 (1 H, t, *J* = 7.6 Hz, CH), 7.92 (1 H, d, *J* = 7.6 Hz, CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 29.2 (Me), 29.8 (Me), 52.3 (NCH_2), 55.7 (MeO), 92.5 (C), 115.2 (2 CH), 121.6 (CH), 122.6 (2 CH), 123.2 (2 CH), 124.2 (CH), 125.8 (CH), 127.2 (CH), 128.6 (2 CH), 130.2 (C), 132.2 (C), 132.7 (CH), 137.3 (C), 144.2 (C), 150.4 (C), 156.7 (C=N), 157.5 (C), 164.6 (C=O), 166.5 (C), 193.4 (C=O). Anal. calcd for $C_{28}H_{24}N_2O_4S$ (484.57): C, 69.40; H, 4.99; N, 5.78; found: C, 69.52; H, 5.12; N, 5.89%.

*1-Benzyl-1,3-dihydro-2*H-*indol-2-one-spiro-1-[4-(*tert-*butylimino)-6-methyl-4*H-*1,3-oxathiin-5-yl]-1-ethanone* (**5e**): Yellow powder; m.p. 162–166 °C; yield 0.72g (92%); IR (KBr) (υ_{max} cm^{-1}): 1743, 1726, 1688, 1578, 1462, 1384, 1272; MS (EI) *m/z* (%): 434 (M$^+$, 10), 391 (68), 57 (100), 43 (100); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (9 H, s, Me_3C), 2.24 (3 H, s, CH_3), 2.33 (3 H, s, CH_3), 4.87 (2 H, s, NCH_2), 7.04 (1 H, t, *J* = 7.5 Hz, CH), 7.18 (1 H, d, *J* = 7.6 Hz, CH), 7.23–7.38 (5 H, m, 5 × CH), 7.68 (1 H, t, *J* = 7.5 Hz, CH), 7.93 (1 H, d, *J* = 7.6 Hz, CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 28.7 (Me), 29.2 (Me), 29.6 (Me_3C), 52.3 (CH_2N), 56.4 (Me_3C), 91.6 (C), 121.6 (CH), 122.7 (2 CH), 125.2 (CH), 125.8 (CH), 126.8 (CH), 128.6 (2 CH), 129.3 (C), 131.4 (C), 132.6 (CH), 137.2 (C), 151.2 (C), 161.6 (C=N), 163.6 (C), 164.8 (C=O), 193.4 (C=O). Anal. calcd for $C_{25}H_{26}N_2O_3S$ (434.55): C, 69.10; H, 6.03; N, 6.45; found: C, 69.23; H, 6.18; N, 6.58%.

*1-Methyl-1,3-dihydro-2*H-*indol-2-one-spiro-[ethyl 6-methyl-4-(*tert-*butylimino)-6-methyl-4*H-*1,3-oxathiine]-5-carboxylate* (**5f**): Yellow powder; m.p. 145–147 °C; yield 0.72g (93%); IR (KBr) (υ_{max} cm^{-1}): 1745, 1725, 1683, 1582, 1466, 1385, 1273; MS (EI) *m/z* (%): 388 (M$^+$, 15), 331 (82), 57 (100); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (9 H, s, Me_3C), 1.32 (3 H, t, *J* = 7.4 Hz, CH_3), 2.34 (3 H, s, CH_3), 3.28 (3 H, s, NCH_3), 4.25 (2 H, q, *J* = 7.4 Hz, CH_2O), 7.06 (1 H, t, *J* = 7.6 Hz, CH), 7.15 (1 H, d, *J* = 7.5 Hz, CH), 7.72 (1 H, t, *J* = 7.5 Hz, CH), 7.83 (1 H, d, *J* = 7.6 Hz, CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.2 (Me), 21.4 (Me), 28.6 (NMe), 29.7 (Me_3C), 55.3 (Me_3C), 61.2 (CH_2O), 91.7 (C), 119.4 (CH), 120.3 (C), 124.3 (CH), 126.2 (CH), 131.6 (C), 132.7 (CH), 150.7 (C), 159.5 (C=N), 163.4 (C=O), 164.7 (C=O), 173.4 (C). Anal. calcd for $C_{20}H_{24}N_2O_4S$ (388.48): C, 61.83; H, 6.23; N, 7.21; found: C, 61.92; H, 6.34; N, 7.32%.

*1-Ethyl-1,3-dihydro-2*H-*indol-2-one-spiro-1-[4-(*tert-*butylimino)-6-methyl-4*H-*1,3-oxathiin-5-yl]-1-ethanone* (**5g**): Yellow powder; m.p. 147–149 °C; yield 0.71g (95%); IR (KBr) (υ_{max} cm^{-1}): 1743, 1728, 1688, 1587, 1469, 1386, 1274; MS (EI) *m/z* (%): 372 (M$^+$, 10), 315 (86), 57 (100); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (9 H, s, Me_3C), 1.37 (3 H, t, *J* = 7.4 Hz, CH_3), 2.26 (3 H, s, CH_3), 2.32 (3 H, s, CH_3), 4.32 (2 H, q, *J* = 7.4 Hz, NCH_2), 7.08 (1 H, t, *J* = 7.5 Hz, CH), 7.33 (1 H, d, *J* = 7.5 Hz, CH), 7.58 (1 H, t, *J* = 7.5 Hz, CH), 7.84 (1 H, d, *J* = 7.5 Hz, CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.8 (Me), 28.3 (Me), 28.7 (Me), 29.2 (Me_3C), 41.8 (NCH_2), 56.7 (Me_3C), 93.4 (C), 122.3 (CH), 124.6 (CH), 125.8 (CH), 129.2 (C), 131.7 (C), 132.3 (CH), 150.8 (C), 161.2 (C=N), 163.8 (C), 164.8 (C=O), 193.5 (C=O). Anal. calcd for $C_{20}H_{24}N_2O_3S$ (372.48): C, 64.49; H, 6.49; N, 7.52; found: C, 64.58; H, 6.57; N, 7.64%.

*1-Benzyl-1,3-dihydro-2*H-*indol-2-one-spiro-1-{4-[(4-bromophenyl)imino]-6-methyl-4*H-*1,3-oxathiin-5-yl}-1-ethanone* (**5h**): Yellow powder; m.p. 196–198 °C; yield 0.91 g (85%); IR (KBr) (υ_{max} cm^{-1}): 1742, 1725, 1698, 1586, 1487, 1382, 1292; MS (EI) *m/z* (%): 534 (M$^+$ + 2, 10), 532 (M$^+$, 10), 490 (68), 43 (100); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.23 (3 H, s, Me), 2.28 (3 H, s, CH_3), 4.85 (2 H, s, NCH_2), 6.95 (1 H, t, *J* = 7.6 Hz, CH), 7.15 (2 H, d, *J* = 7.8 Hz, 2 × CH), 7.24 (1 H, d, *J* = 7.6 Hz, CH), 7.23–7.34 (5 H, m, 5 × CH), 7.65 (1 H, t, *J* = 7.6 Hz, CH), 7.94 (1 H, d, *J* = 7.6 Hz, CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 28.4 (Me), 28.6 (Me), 52.5 (NCH_2), 92.7 (C), 118.7 (C), 121.7 (CH), 122.7 (2 CH), 123.9 (CH), 125.4 (2 CH), 125.8 (CH), 126.2 (CH), 128.8 (2 CH), 130.4 (C), 132.3 (C), 132.8 (2 CH), 133.2 (CH), 136.7 (C), 150.6 (C), 151.8 (C), 156.7 (C=N), 164.7 (C=O), 165.8 (C), 193.7 (C=O). Anal. calcd for $C_{27}H_{21}BrN_2O_3S$ (533.44): C, 60.79; H, 3.97; N, 5.25; found: C, 60.82; H, 4.12; N, 5.37%.

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References

1 S.N. Pandeya, S. Smitha, M. Jyoti and S.K. Sridhar, *Acta Pharm.*, 2005, **55**, 27.
2 L.V. Kara, M.L. Julie, R. Marie, G.P. Stephen and B.B. John, *J. Med. Chem.*, 2007, **50**, 5109.
3 R. Hajinasiri, Z. Hossaini and F. Sheikholeslami-Farahani, *Combinat. Chem. High Throughput Screening*, 2015, **18**, 42.
4 Z. Hossaini, S. Soltani, F. Sheikholeslami-Farahani, S.Z. Sayyed-Alangi and H. Sajjadi-Ghotabadi, *Chem. Heterocycl. Compd*, 2015, **51**, 26.
5 Z. Hossaini, F. Rostami-Charati, M. Ghasemian and S. Afshari Sharif Abad, *Synlett*, 2015, **26**, 1222.
6 Z. Hossaini, F. Rostami-Charati, M. Ghambarian and S. A. Siadati, *Phosphorus, Sulfur, Silicon Rel. Elem.*, 2015, **190**, 1177.
7 P. Slobbe, E. Ruijter and R.V.A. Orru, *Med. Chem. Commun.*, 2012, **3**, 1189.
8 V.D.G. Heijden, E. Ruijter and R.V.A. Orru, *Synlett*, 2013, 666.
9 C. Hulme, M. Ayaz, G. Martinez-Ariza, F. Medda and A. Shaw, in *Small molecule medicinal chemistry: strategies and technologies*, eds W. Czechtizky and P. Hamley, Wiley-VCH, Weinheim, 2015, chap. 6.
10 A. Gollner, *Synlett*, 2015, 426.
11 R.T. Brown, *Indoles, the monoterpenoid indole alkaloids*, Wiley, New York, 1983, Vol. 25.
12 C.V. Galliford and K.A. Scheidt, *Angew. Chem. Int. Ed.*, 2007, **46**, 8748.
13 G.S. Singh and Z.Y. Desta, *Chem. Rev.*, 2012, **112**, 6104.
14 M.M.M. Santosa, *Tetrahedron*, 2014, **70**, 9735.
15 T.L. Pavlovska, R.Gr. Redkin, V.V. Lipson and D.V. Atamanuk, *Mol. Divers.*, 2016, **20**, 299.
16 H. Ishikawa, T. Suzuki and Y. Hayashi, *Angew. Chem. Int. Ed.*, 2009, **48**, 1304.
17 A. Ziyaei Halimehjani, K. Marjani and A. Ashouri, *Green. Chem.*, 2010, **12**, 1306.
18 A.E. Wahba and M.T. Hamann, *Mar. Drugs*, 2010, **8**, 2395.
19 C. Vaxelaire, P. Winter and M. Christmann, *Angew. Chem. Int. Ed.*, 2011, **50**, 3605.
20 W. Zhao and F.E. Chen, *Curr. Org. Synth.*, 2012, **6**, 873.
21 F. Xiang, M. Stuart, J. Vorenkamp, S. Roest, H. Timmer-Bosscha, M.C. Stuart, R. Fokkink and T. Loontjens, *Macromolecules*, 2013, **46**, 4418.
22 A. Ali, A.G. Correa, D. Alves, J. Zukerman-Schpector, B. Westermann, M.A.B. Ferreira and M.W. Paixao, *Chem. Commun.*, 2014, 11926.
23 A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, 2000, **9**, 3168.
24 C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **10**, 51.
25 I. Akritopolou-Zanze, *Curr. Opin. Chem. Biol.*, 2008, **12**, 324.
26 A. Dömling, W. Wang and K. Wang, *Chem. Rev.*, 2012, **112**, 3083.
27 A. Dömling and T. Zarganes-Tzitzikas, *Org. Chem. Front.*, 2014, **1**, 834.
28 Z. Hossaini, M. Ghambarian, S. Afshari Sharif Abad and B. Mohtat, Lett. Org. Chem., 2015, **12**, 176.
29 S.Z. Sayyed Alangi and Z. Hossaini, *Chem. Heterocycl. Compd*, 2015, **51**, 541.
30 C.J. Li, *Chem. Rev.*, 2005, **105**, 3095.
31 S. Kobayashi and K. Manabe, *Acc. Chem. Res.*, 2002, **35**, 209.
32 U.M. Lindstrom, *Chem. Rev.*, 2002, **102**, 2751.
33 A. Solhy, A. Elmakssoudi, R. Tahir, M. Karkouri, M. Larzek, M. Bousmina and M. Zahouily, *Green Chem.*, 2010, **12**, 2261.
34 P.A. Grieco, ed., *Organic synthesis in water*, Blackie Academic and Professional, London, 1998.

35 P.T. Anastas and J.C. Warner, *Green chemistry: theory and practice*, Oxford University Press, New York, 1988.
36 M. Lancester, *Green chemistry: an introductory text*, Royal Society of Chemistry, Cambridge, 2002.
37 J.N. Tan, H. Li and Y. Gu, *Green Chem*., 2010, **12**, 1772.
38 M. Sabbaghan, A. Anaraki Firooz and V. Jan Ahmadi, *J. Mol. Liq.*, 2012, **175**, 135.
39 H.R. Shaterian and M. Mohammadnia, *J. Mol. Liq.*, 2013, **177**, 353.
40 F. Rostami-Charati, Z. Hossaini, F. Sheikholeslami-Farahani, Z. Azizi and S.A. Siadati, *Combinat. Chem. High Throughput Screening*, 2015, **18**, 872.
41 J. Goerdeler, A. Laqua and Ch. Lindner, *Chem. Ber.*, 1974, **107**, 3518.
42 W. Walter and T. Fleck, *Liebigs Ann. Chem*., 1976, 670.
43 S.J. Garden, J.C. Torres, L.E. da Silva and A.C. Pinto, *Synth. Commun*., 1998, **28**, 1679.