Chemical Methodologies 3(2019) 237-250

Chemical Methodologies

Journal homepage: http://chemmethod.com

Original Research article

An Efficient Method for Synthesis of Some Novel Spiro[indoline-thiazolidine]dione Derivatives

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ARTICLE INFORMATION

Received: 16 September 2018
Received in revised: 03 October 2018
Accepted: 27 October 2018
Available online: 29 October 2018

DOI: 10.22034/chemm.2018.149025.1088

KEYWORDS

Spiro compounds
Isatin
Cyclocondensation
Schiff base
Mercapto acetic acid

ABSTRACT

A facile synthesis of eighteen's novel derivatives of spiro[indole-thiazolidine]diones (**5a-5r**) has been developed *via* hitherto unknown schiff bases. In the first step, we alkylated the isatin ring using different alkyl halides in DMF and in the presence of potassium carbonate and *tert*-butyl ammonium bromide to get 1a-1i. In the second step, *N*-substituted isatin (**1a-1i**) reacted with different amine compounds (**2a-2f**) to get schiff base intermediates (**3a-3r**). In the third step, cyclocondensation reaction with mercaptoacetic acid afforded a new class of spiro diones. The amine moieties which are used in the second step of this synthesis are varied from aniline derivatives (**2a-2d**), phenylpyrazole (**2e**) and oxazole (**2f**) analogues. Of the 18 final new compounds 9 analogues derived from aniline, 2 analogues derived from oxazole and 7 of them synthesized from phenylpyrazole analogues. Chemical structures of all new compounds were confirmed by spectroscopic methods such as IR, HNMR and CNMR.

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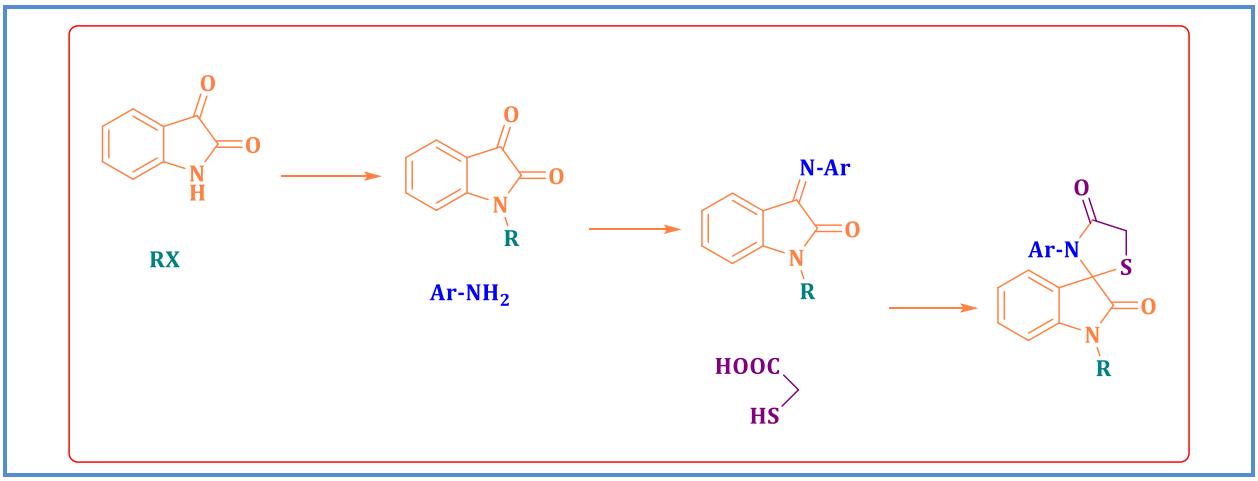
Graphical Abstract



Introduction

Indole and its analogeous are good pharmacophores for designing several chemotherapeutic reagents which show a wide spectrum of antimicrobial activities (1). The 3-substituted indole nucleuses substructures are notable for their unique three-dimensional structures (2) which are presented in a number of pharmaceuticals and natural products such as gelsemine, horsfiline, gelseverine, rhynchophylline and elacomine, etc. (Figure 1) (3).

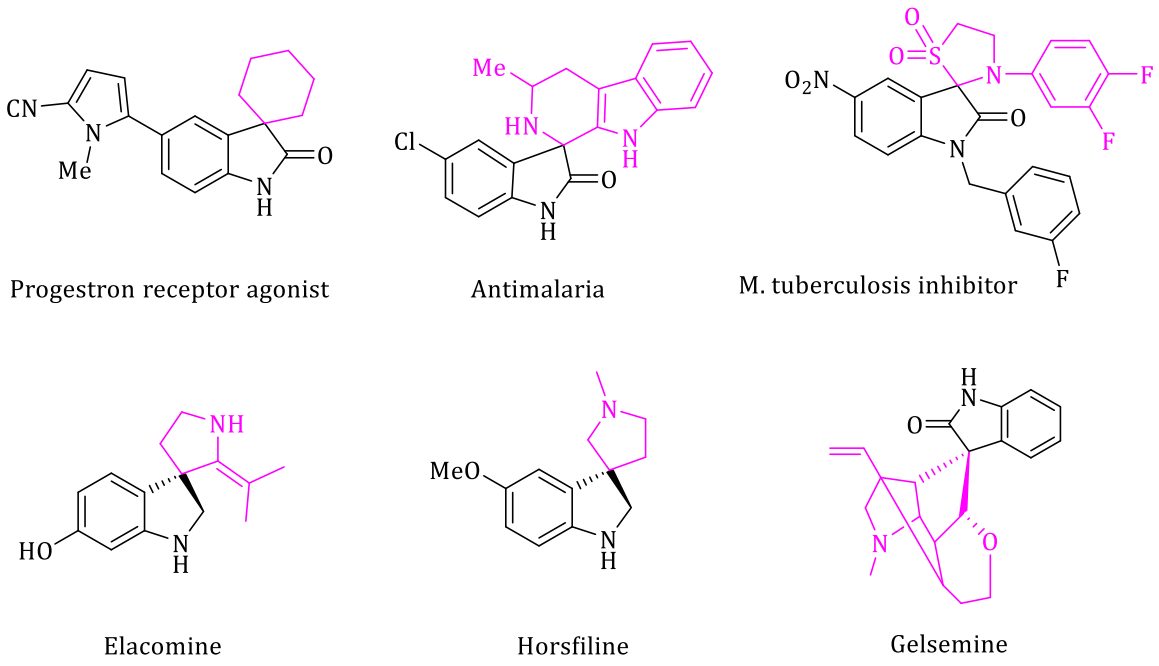


Figure 1. Selected examples of natural products and biologically important compounds with spiro-linked oxindole motif

The unique structural framework and the highly distinct pharmacological activity exhibited by spiro-oxindole compounds have made them attractive synthetic targets (4). Isatin and its derivatives have different biological effects, including antituberculosis (5), anticancer (6, 7), anti-HIV (8), anti-inflammatory, antibacterial (9), antiviral (10) and anticonvulsant (11, 12). Isatin is a synthetically flexible substrate, which can be used for the synthesis of large varieties of schiff base transition metal complex derivatives (13) and heterocyclic compounds. Also, it is used as a starting material for various drug syntheses.

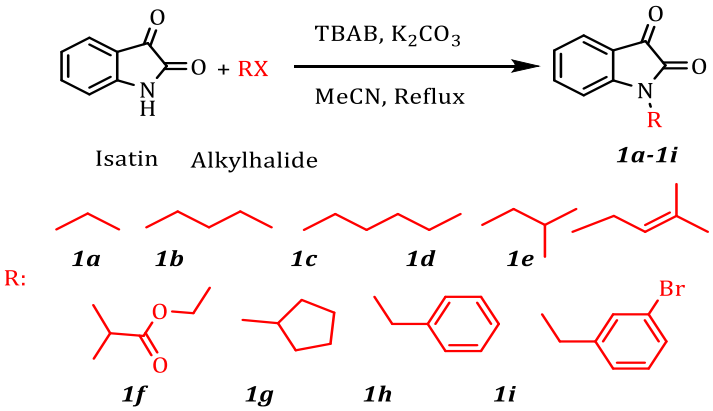
Based on our interest in the synthesis of constructing spiro-oxindole structural framework and in continuation of our work on the synthesis of spiro-oxindole derivatives (14, 15), here, we introduced a new class of the spiro[indole-thiazolidine]diones. For this purpose, we run some chemical reactions of various arylimino-2H-indol-2-ones with mercapto-acetic acid.

Experimental

All chemicals were obtained from Merck (Germany) or Fluka (Switzerland) and other chemical companies. All yields refer to isolated products after chromatography and other indicated purification methods. Infrared (IR) spectra were run on a Shimadzu FTIR-8300 spectrophotometer; ν_{max} in cm^{-1}. The ^{1}H NMR (300 MHz) and ^{13}C NMR (62.5 MHz) were run on a Bruker advanced DPX-250, FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard in pure deuterated solvents ($CDCl_3$, DMSO-d_6 and D_2O). Melting points were recorded on a Büchi B 545 apparatus in open capillary tubes and are uncorrected.

General procedure for synthesis of *N*-alkylisatines (1a-1i)

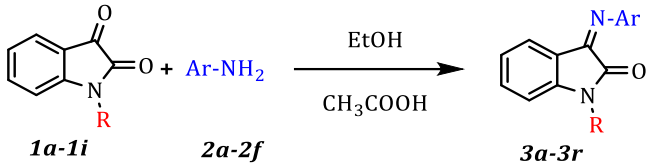
The synthesis of *N*-substituted isatin derivatives are considered, as prospective precursors in the present study. *N*-alkylated isatins (**1a-1i**) were prepared using potassium carbonate and *tert*-butyl ammonium bromide (TBAB) in acetonitril and revealed that the method is suitable for the preparation of all *N*-substituted isatins (Scheme 1).

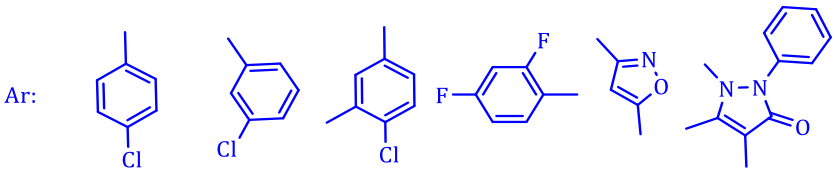


Scheme 1: Synthesis of alkylated isatine **(1a-1i)**

General procedure for synthesis of isatin schiff bases (3a-3r)

A mixture of *N*-substituted isatin (**1a-1i**) (2 mmol) and different amine compounds (**2a-2f**) (0.406 g, 2 mmol) in absolute ethanol (20 mL) along with 2–3 drops of glacial acetic acid was stirred at room temperature. An orange colored solid that was separated out after 10 min of stirring was filtered, dried and recrystallized from ethanol to give schiff's base (3a-3r) as orange crystals (Scheme 2).





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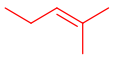
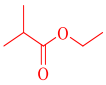
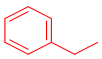
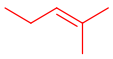
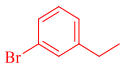
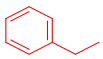
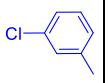
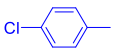
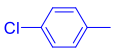
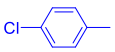
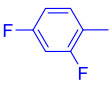
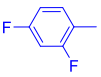
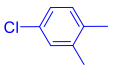
R									
Ar									
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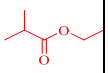
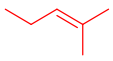
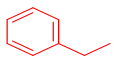
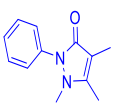
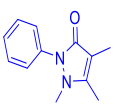
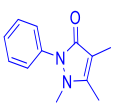
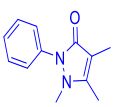
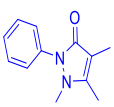
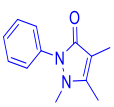
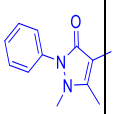
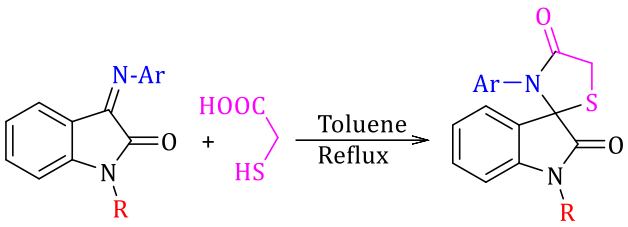
R									
Ar									

Scheme 2: Synthesis of isatin schiff bases (**3a-3r**)

General procedure for synthesis of spiro[indoline-thiazolidine]dione (5a-5r)

A mixture of 3-indolyl imine (**3a-3r**) (2.0 mmol) and mercaptoacetic acid (**4**) (0.23 g, 2.6 mmol) was refluxed in dry toluene for 8 h, with concurrent removal of water azeotropically, using dean-stark apparatus. The solution turned light yellow and a sticky yellow solid was formed. The solvent

was removed under reduced pressure and the remains were treated with saturated the solution of sodium bicarbonate, to remove the unreacted acid. The solid was filtered, dried and crystallized from methanol–chloroform mixture to obtain 5a-5r as colorless crystals in 65–85% yield (Scheme 3).



3a-3r **4** **5a-5r**

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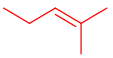
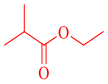
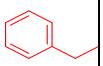
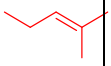
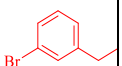
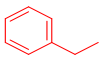
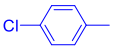
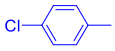
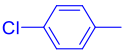
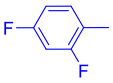
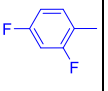
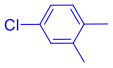
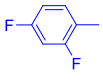
R									
Ar									
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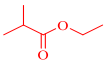
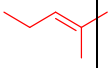
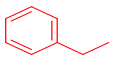
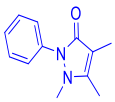
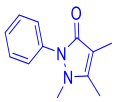
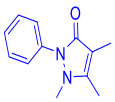
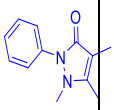
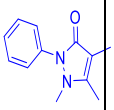
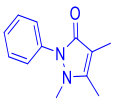
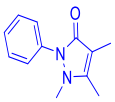
R									
Ar									

Scheme 3. Synthesis of spiro[indoline-3,2'-thiazolidine]-2,4'-dione (**5a-5r**)

Spectral data of products

3'-(3-chlorophenyl)-1-ethyl spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5a)

White solid, yield: 75%, IR (KBr) (ν_{max}/cm^{-1}): 3663 (C-H, aromatic), 3062, 2994 (C-H, aliphatic), 1711 (C=O, thiazolidine ring), 1612 (C=O, cyclic amide), 1347, 1466 (C=C, alkene), 1346, 1249 (C-N stretch), 745, 746 (C-H bending), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), δ=6.58-7.26 (m, 8H, ArH), 4.22 (d, 1H, CH_2-S, *J*=15 Hz), 3.74 (d, 1H, CH_2-S,*J*=15 Hz), 3.61-3.74 (m, 2H, CH_2CH_3), 0.89 (t, 3H, CH_2CH_3, *J*= 6

Hz). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=174.1, 171.4, 169.8, 164.3, 156.5, 151.7, 143.1, 130.8, 125.4, 124.4, 123.0, 113.7, 109.2, 96.3, 67.8, 40.3, 29.1, 13.7.

1-Butyl-3'-(4-chlorophenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5b)

White solid, yield: 80%, IR (KBr) (ν_{max}/cm^{-1}): 3234 (C-H, aromatic), 2959 (C-H, aliphatic), 1721, 1612 (C=O amide), 1495, 1468 (C=C, alkene), 1350 (C-N stretch, aromatic), 762, 685 (C-H bending), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), *δ*=6.58-7.26 (m, 8H, ArH), 4.23 (d, 1H, CH_2-S, *J*=15 Hz), 3.74 (d, 1H, CH_2-S, *J*=15 Hz), 3.65-3.70 (m, 2H, N-$CH_2CH_2CH_2CH_3$), 1.55-1.67 (m, 2H, N-$CH_2CH_2CH_2CH_3$), 1.33-1.40 (m, 2H, N-$CH_2CH_2CH_2CH_3$), 0.89 (t, 3H, N-$CH_2CH_2CH_2CH_3$, *J*=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=174.1, 171.4, 169.8, 164.3, 156.5, 151.7, 143.1, 130.8, 125.4, 124.4, 123.0, 113.7, 19.2, 96.3, 67.8, 40.3, 29.1, 13.7.

3'-(4-chlorophenyl)-1-pentyl spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5c)

White solid, yield: 80%, mp: IR (KBr) (ν_{max}/cm^{-1}): 3646 (C-H, aromatic), 3083, 3030 (C-H, aliphatic), 1703 (C=O, thiazolidine ring), 1611 (C=O, cyclic amides), 1357, 1458 (C=C, alkene), 1376, 1210 (C-N stretch), 775, 740 (C-H bending), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), *δ*=6.88-7.42 (m, 8H, ArH), 4.28 (d, 1H, CH_2-S, *J*=15 Hz), 3.79 (d, 1H, CH_2-S, *J*=15 Hz), 3.56-3.62 (m, 2H, $CH_2CH_2CH_2CH_2CH_3$), 1.43-1.47 (m, 2H, $CH_2CH_2CH_2CH_2CH_3$), 1.19-1.24 (m, 2H, $CH_2CH_2CH_2CH_2$-CH_3), 1.06-1.10 (m, 2H, $CH_2CH_2CH_2CH_2CH_3$), 0.79 (t, 3H, $CH_2CH_2CH_2CH_2CH_3$, *J*=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=174.6, 172.7, 142.9, 134.5, 131.4, 130.0, 129.5, 126.4, 124.6, 123.4, 121. 2, 116.2, 109.3, 65.1, 40.4, 32.9, 28.7, 26.7, 22.2, 13.9.

3'-(4-chlorophenyl)-1-(3-methylbut-2-en-1-yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5d)

White solid, yield: 75%, IR (KBr) (ν_{max}/cm^{-1}): 3452 (C-H, aromatic), 2913 (C-H, aliphatic), 1718, 1612 (C=O amide), 1491 (C=C, alkene), 1342 (C-N stretch, aromatic), 731, 570 (C-H bending), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), *δ*=6.68-7.48 (m, 8H, ArH), 4.90-4.92 (m, 1H, CH_2-CH=C), 4.39 (d, 1H, CH_2-S, *J*=15 Hz), 4.14-4.31 (m, 2H, N-CH_2), 3.88 (d, 1H, CH_2-S, *J*=15 Hz), 1.80 (s, 3H, CH_3), 1.71 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=174.3.9, 172.4, 142.7, 137.8, 134.4, 131.3, 129.7, 129.6, 129.4, 126.2, 124.6, 123.4, 117.0, 109.7, 69.9, 38.4, 32.9, 25.6, 18.1.

Ethyl 2-(3'-(2,4-difluorophenyl)-2,4'-dioxospiro[indoline-3,2'-thiazolidin]-1-yl) propanoate (5e)

White solid, yield: 60%, IR (KBr) (ν_{max}/cm^{-1}): 3072 (C-H, aromatic), 2936 (C-H, aliphatic), 1711, (C=O, ester), 1612 (C=O, amide), 1512, 1491 (C=C, alkene), 1280 (C-N stretch, aromatic), 757, 692 (C-H bending). ^{1}H NMR (300 MHz, $CDCl_3$-*d*), *δ*=6.58-7.28 (m, 7H, ArH), 4.39 (m, 1H, N-CH-CH_3), 3.88 (d, 1H, CH_2-S,*J*=15 Hz), 3.61-3.74 (m, 3H, CH_2-S, CH_3-CH_2-O), 1.58 (d, 3H, N-CH-CH_3, *J*=9 Hz), 0.95 (t, 3H, CH_3-CH_2-O, *J*=9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=174.8, 172.0, 142.8, 131.4, 126.5, 126.4, 123.8, 123.3, 112.1, 112.0, 111.7, 109.0, 106.5, 106.2, 104.8, 69.5, 40.1, 32.9, 29.1, 19.9, 13.6.

1-Benzyl-3'-(3-chlorophenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5f)

White solid, yield: 80%, IR (KBr) (ν_{max}/cm^{-1}): 3388 (C-H, aromatic), 3061, 2974 (C-H, aliphatic), 1712 (C=O, thiazolidine ring), 1612 (C=O, cyclic amide), 1360, 1408 (C=C, alkene), 1386, 1229 (C-N stretch), 765, 746 (C-H bending), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), *δ*=7.52 (d, 1H, ArH, *J*=6 Hz), 6.92-7.8 (m, 11H, ArH), 6.60 (d, 1H, ArH, *J*=6 Hz), 4.66 (d, 1H, CH_2-S, *J*=12 Hz), 4.66 (d, 1H, CH_2-S, *J*=12 Hz), 4.42 (d, 1H, CH_2-Ph,*J*=12 Hz), 3.91 (d, 1H, CH_2-Ph,*J*=12 Hz). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=174.7, 172.5, 142.4, 137.0, 134.8, 134.4, 131.4, 130.3, 128.9, 127.8, 126.8, 126.3, 124.3, 123.7, 110.2, 70.0, 44.0, 32.0.

3'-(2,4-difluorophenyl)-1-(3-methylbut-2-en-1-yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5g)

White solid, yield: 65%, IR (KBr) (ν_{max}/cm^{-1}): 3430 (C-H, aromatic), 2998 (C-H, aliphatic), 1716, 1611 (C=O), 1510, 1489 (C=C, alkene), 1298.4 (C-N stretch, aromatic), 975, 754 (C-H bending), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), *δ*=6.68-7.53 (m, 7H, ArH), 4.92-5.01 (m, 1H, N-CH_2-CH=), 4.19-4.36 (m, 3H, N-CH_2-CH=, CH_2-S), 3.88 (d, 1H, CH_2-S,*J*=15 Hz), 1.83 (s, 3H, =C-$(CH_3)_2$), 1.73 (s, 3H, =C-$(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=171.9, 142.6, 137.8, 131.4, 126.3, 126.2, 123.8, 123.4, 117.1, 112.0, 111.9, 111.7, 111.6, 109.4, 105.1, 104.8, 69.5, 38.5, 32.9, 25.6, 18.1.

1-(3-bromobenzyl)-3'-(5-chloro-2-methylphenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5h)

White solid, yield: 80%, IR (KBr) (ν_{max}/cm^{-1}): 3424 (C-H, aromatic), 2980 (C-H, aliphatic), 1636, 1616 (C=O amide), 1581, 1523 (C=C, alkene), 1280 (C-N stretch, aromatic), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), *δ*=6.76-7.35 (m, 11H, ArH), 4.98 (d, 1H, CH_2-ph, *J*=12 Hz), 4.79 (d, 1H, CH_2-ph,*J*=12 Hz), 4.42 (d, 1H, CH-S, *J*=12 Hz), 3.93 (d, 1H, CH-S, *J*=12 Hz), 2.07 (s, 3H, CH_3 related to phenyl ring). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=175.7, 172.2, 167.4, 142.4, 142.4, 142.2, 139.8, 138.7, 137.6, 130.9, 129.1, 127.2, 125.0, 123.5, 123.4, 108.1, 98.2, 70.4, 59.9, 40.0, 32.9, 29.2, 19.9, 13.7, 10.9.

1-Benzyl-3'-(2,4-difluorophenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5i)

White solid, yield: 63%, IR (KBr) (ν_{max}/cm^{-1}): 3479 (C-H, aromatic), 3388, 3252 (C-H, aliphatic), 1715 (C=O, thiazolidine ring), 1682 (C=O, cyclic amide), 1369, 1458 (C=C, alkene), 1346, 1239 (C-N stretch), 765, 733 (C-H bending), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), δ=6.62-7.57 (m, 12H, ArH), 4.98 (d, 1H, CH_2-S, *J*=12 Hz), 4.79 (d, 1H, CH_2-S, *J*=12 Hz), 4.42 (d, 1H, CH_2-Ph, *J*=12 Hz), 3.93 (d, 1H, CH_2-Ph, *J*=12 Hz). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), δ=172.0, 163.9, 161.4, 142.4, 134.6, 131.5, 130.8, 130.7, 128.8, 127.9, 127.1, 126.5, 126.4, 123.7, 119.8, 112.1, 109.8, 105.5, 105.3, 105.0, 69.9, 44.0, 32.9.

Ethyl-2-(3'-(5-methylisoxazol-3-yl)-2,4'-dioxospiro[indoline-3,2'-thiazolidin]-1yl) propanoate (5j)

White solid, yield: 83%, IR (KBr) (ν_{max}/cm^{-1}): 3790 (C-H, aromatic), 2966 (C-H, aliphatic), 1736 (C=O, ester), 1604 (C=O, amide), 1491, 1445 (C=C, alkene), 1368 (C-N stretch, aromatic), 810, 751 (C-H bending), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), δ=7.88 (s, 1H, ArH), 6.58-7.28 (m, 4H, ArH), 4.96 (m, 1H, N-CH-CH_3), 4.22 (d, 1H, CH_2-S, *J*=15 Hz), 3.65-3.77 (m, 3H, CH_2-S and CH_2-O), 2.21 (s, 3H, CH_3 related to isoxazole ring), 1.35 (t, 3H, O-CH_2CH_3, *J*=6 Hz), 0.87 (d, 3H, N-CH-CH_3, *J*=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), δ=174.1, 171.4, 169.8, 163.1, 156.5, 143.1, 130.8, 125.4, 124.4, 123.0, 109.2, 96.3, 67.8, 40.3, 32.7, 29.1, 20.0, 13.7, 12.4.

1-Butyl-3'-(5-methylisoxazol-3-yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5k)

White solid, yield: 75%, IR (KBr) (ν_{max}/cm^{-1}): 3312 (C-H, aromatic), 2998 (C-H, aliphatic), 1642 (C=O), 1612 (C=O, amide), 1581, 1523 (C=C, alkene), 1280 (C-N stretch, aromatic), 752, 695 (C-H bending), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), δ=6.80-7.28 (m, 4H, ArH), 6.58 (s, 1H, related to isoxazole ring) 4.22 (d, 1H, CH_2-S, *J*=15 Hz), 3.74 (d, 1H, CH_2-S, *J*=15 Hz), 3.65-3.70 (m, 2H, N-$CH_2CH_2CH_2CH_3$), 2.21 (s, 3H, CH_3 related to isoxazole ring), 1.55-1.67 (m, 2H, N-$CH_2CH_2CH_2CH_3$), 1.33-1.40 (m, 2H, N-$CH_2CH_2CH_2CH_3$), 0.89 (t, 3H, CH_3, *J*=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), δ=174.1, 171.4, 189.8, 168.5, 143.1, 130.8, 125.4, 124.4, 123.3, 109.2, 96.3, 77.4, 77.0, 76.8, 68.6, 43.3, 32.7, 29.1, 20.0, 13.7, 12.4.

1-Butyl-3'-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5l)

White solid, yield: 85%, IR (KBr) (ν_{max}/cm^{-1}): 3434 (C-H, aromatic), 2957 (C-H, aliphatic), 1721, 1645, 1612 (C=O amide), 1490, 1468 (C=C, alkene), 1360 (C-N stretch, aromatic), 752, 695 (C-H bending). ^{1}H NMR (300 MHz, $CDCl_3$-*d*), δ=7.10-7.39 (m, 9H, ArH), 4.22 (d, 1H, CH_2-S, *J*=15 Hz), 3.74 (d, 1H, CH_2-S, *J*=15 Hz), 3.65-3.70 (m, 2H, N-$CH_2CH_2CH_2CH_3$), 3.02 (s, 3H, N-CH_3), 2.16 (s, 3H, =C-CH_3), 1.55-1.67 (m, 2H, N-$CH_2CH_2CH_2CH_3$), 1.33-1.40 (m, 2H, N-$CH_2CH_2CH_2CH_3$), 0.89 (t, 3H,

$CH_2CH_2CH_2CH_3$, *J*=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=175.3, 172.2, 161.9, 153.9, 142.3, 137.4, 134.5, 131.0, 129.2, 125.0, 123.5, 117.4, 106.5, 60.4, 38.4, 35.0, 32.9, 25.7, 18.2, 14.2, 10.7

3'-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-1-pentyl spiro [indoline-3,2'-thiazolidine]-2,4'-dione (5m)

White solid, yield: 82%, IR (KBr) (ν_{max}/cm^{-1}): 3389 (C-H, aromatic, stretch), 3065 (C-H, aliphatic, stretch), 1715 (C=O, thiazolidine ring), 1656, 1612 (C=O, cyclic amide), 1565 (C=C, alkene), 1344, 1288 (C-N stretch), 757, 743 (C-H bending). ^{1}H NMR (300 MHz, $CDCl_3$-*d*), *δ*=6.59-7.28 (m, 8H, ArH), 4.22 (d, 1H, CH_2-S, *J*=15 Hz), 3.74 (d, 1H, CH_2-S, *J*=15 Hz), 3.65-3.70 (m, 2H, N-CH_2CH_3), 0.88 (T, 3H, N-CH_2CH_3, *J*=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=174.1, 171.4, 169.8, 164.3, 156.5, 151.7, 143.1, 130.8, 125.4, 124.4, 123.0, 113.7, 109.2, 96.3, 67.8, 40.3, 29.1, 13.7.

1-(sec-butyl)-3'-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)spiro [indoline -3,2'-thiazolidine]-2,4'-dione (5n)

White solid, yield: 80%, IR (KBr) (ν_{max}/cm^{-1}): 3450 (C-H, aromatic), 2998 (C-H, aliphatic), 1715, 1665, 1611 (C=O, amide), 1487, 1346 (C=C, alkene), 1285 (C-N stretch, aromatic), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), *δ*=6.76-7.38 (m, 9H, ArH), 4.32 (d, 1H, CH_2-S, *J*=12 Hz), 3.82 (d, 1H, CH_2-S, *J*=12 Hz), 3.65-3.69 (m, 1H, N-CH_3CH CH_2CH_3), 3.00 (s, 3H, N-CH_3), 2.21 (s, 3H, =C-CH_3), 1.65 (m, 2H, N-CH_3CH CH_2CH_3), 1.34 (d, 3H, N-CH_3CH CH_2CH_3, *J*=6Hz), 0.89 (t, 3H, N-CH_3CH CH_2CH_3, *J*=6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=175.7, 172.2, 167.4, 142.4, 142.2, 139.8, 137.4, 138.7, 134.6, 130.9, 129.1, 127.2, 125.0, 123.5, 123.4, 108.1, 98.2, 70.4, 59.9, 40.0, 32.9, 29.2, 19.9, 13.7, 10.9.

3'-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-1-(3-methylbut-2-en-1-yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5o)

White solid, yield: 90%, IR (KBr) (ν_{max}/cm^{-1}): 3465 (C-H, aromatic, stretch), 2391 (C-H, aliphatic, stretch), 1715 (C=O, thiazolidine ring), 1674, 1613 (C=O, cyclic amides), 1367, 1468 (C=C, alkene), 1346, 1229 (C-N stretch), 755, 695 (C-H bending). ^{1}H NMR (300 MHz, $CDCl_3$-*d*), *δ*=6.73-7.41 (m, 9H, ArH), 5.13-5.20 (m, 1H, CH_2-CH=C$(Me)_2$), 4.36 (d, 1H, CH_2-S, *J*=12 Hz), 4.11-4.16 (m, 2H, CH_2-CH=C$(Me)_2$), 3.86 (d, 1H, CH_2-S, *J*= 12 Hz) 3.02 (s, 3H, N-CH_3) 2.12 (s, 3H, =C-CH_3, related to pyrazole ring), 1.85 (s, 3H, CH_2-CH=C$(Me)_2$), 1.75 (s, 3H, CH_2-CH=C$(Me)_2$). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), *δ*=175.3, 172.2, 168.2, 161.9, 153.9, 142.3, 137.5, 134.5, 131.0, 129.4, 129.2, 128.8, 127.2, 125.1, 125.0, 123.5, 123.3, 117.4, 108.5, 60.4, 38.4, 32.9, 25.9, 25.7, 18.2, 14.2, 10.7.

1-Cyclopentyl-3'-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl) spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5p)

White solid, yield: 75%, IR (KBr) (ν_{max}/cm^{-1}): 3450 (C-H, aromatic, stretch), 2977 (C-H, aliphatic, stretch), 1713 (C=O, thiazolidine ring), 1660, 1611 (C=O, cyclic amide), 1486, 1466 (C=C, alkene), 1342, 1219 (C-N stretch), 755, 699 (C-H bending), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), δ=6.75-7.33 (m, 9H, ArH), 4.53-4.62 (m, 1H, N-CH-C_4H_8), 4.27 (d, 1H, CH_2-S, *J*=12 Hz), 3.77 (d, 1H, CH_2-S, *J*=12 Hz) 2.93 (s, 3H, N-CH_3), 1.60-2.13 (m, 11H, =C-CH_3, N-CH-C_4H_8). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), δ=172.3, 163.9, 148.2, 141.9, 134.5, 130.8, 129.2, 127.2, 124.9, 123.2, 121.7, 110.3, 109.3, 69.5, 53.0, 35.1, 33.0, 31.6, 27.8, 25.1, 14.1, 10.7.

1-benzyl-3'-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione(5q)

White solid, yield: 78%, IR (KBr) (ν_{max}/cm^{-1}): 3112 (C-H, aromatic, stretch), 2926 (C-H, aliphatic, stretch), 1720, 1673.7, 1613 (C=O, cyclic amide), 1581.2, 1523 (C=C, alkene), 1360, 1185 (C-N stretch), 750, 697 (C-H bending). ^{1}H NMR (300 MHz, $CDCl_3$-*d*), δ=7.15-7.39 (m, 14H, ArH), 4.55 (s, 2H, CH_2-ph), 4.33 (d, 1H, CH_2-S, *J*=9 Hz), 3.84 (d, 1H, CH_2-S, *J*=9 Hz), 3.02 (s, 3H, CH_3), 2.05 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$-*d*), δ=174.1, 171.4, 169.8, 163.1, 161.3, 160.8, 156.5, 151.7, 145.8, 143.1, 137.2, 130.8, 126.6, 125.4, 124.4, 123.0, 113.7, 109.2, 96.3, 67.8, 57.4, 32.7, 29.1, 12.4.

1-Ethyl-3'-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione(5r)

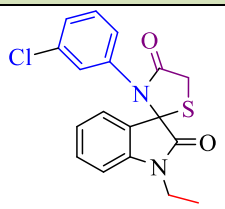
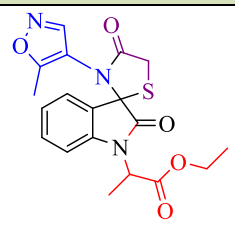
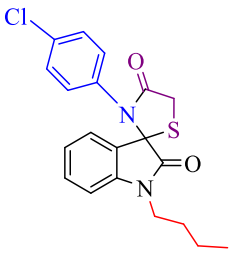
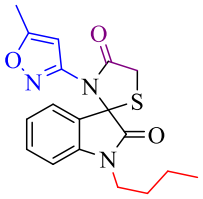
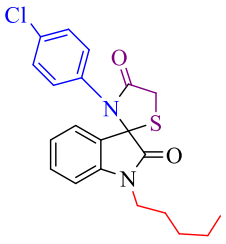
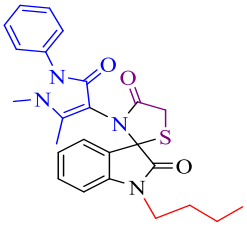
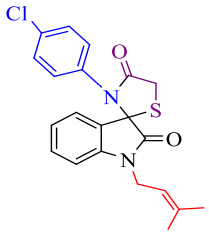
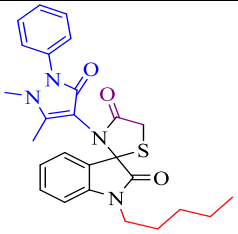
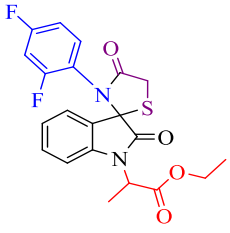
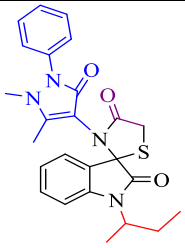
White solid, yield: 80%, IR (KBr) (ν_{max}/cm^{-1}): 3733 (C-H, aromatic), 2991 (C-H, aliphatic), 1713 (C=O, thiazolidine ring), 1656, 1613 (C=O, cyclic amides), 1367, 1468 (C=C, alkene), 1356, 1219 (C-N stretch), 755, 743 (C-H bending), ^{1}H NMR (300 MHz, $CDCl_3$-*d*), δ=7.98 (d, 1H, ArH, *J*=6 Hz) 7.09-7.41 (m, 7H, ArH), 6.79 (d, 1H, ArH, *J*=6 Hz) 4.36 (d, 1H, CH_2-S, *J*=12 Hz), 3.86 (d, 1H, CH_2-S, *J*=12 Hz) 3.72-3.80 (m, 2H, CH_2-CH_3) 3.00 (s, 3H, N-CH_3) 2.15 (s, 3H, =C-CH_3, related to pyrazole ring), 1.27 (t, 3H, CH_2-CH_3, *J*=6 Hz), ^{13}C NMR (75 MHz, $CDCl_3$-*d*), δ=175.4, 172.3, 153.8, 142.0, 134.5, 131.0, 129.2, 129.0, 127.3, 126.8, 125.2, 125.0, 124.4, 123.5, 123.4, 121.9, 108.0, 69.5, 35.2, 35.1, 12.6, 10.8.

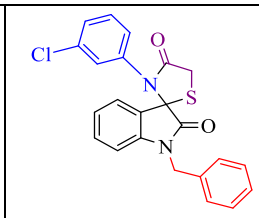
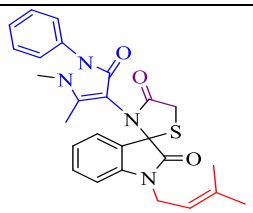
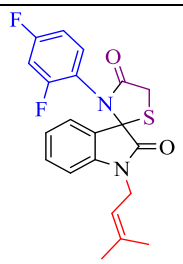
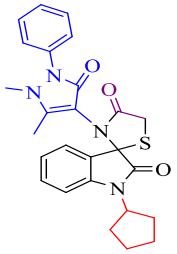
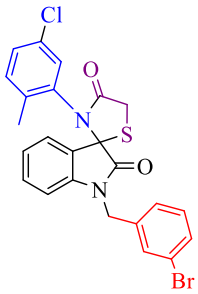
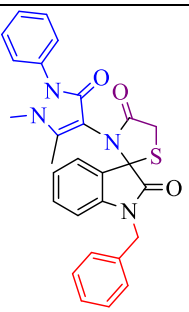
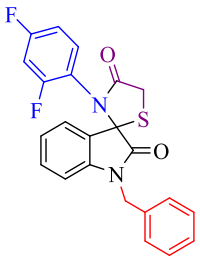
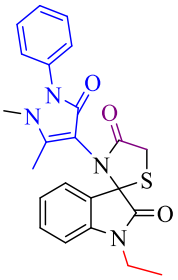
Result and Discussion

As a part of our continuing attention on the synthesis of new spiro heterocycles by molecular and catalytically modification (1, 2), we have undertaken the facile and well-designed synthesis of novel spiro heterocycles (5a-5r) *via* hitherto unknown schiff's bases, (3a–3r) in 80–95% yield (Scheme 2). In this process, the schiff's bases were synthesized by the reaction of indol-2,3-dione (1a–1i) with threedifferent sources of amine including 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one,

aniline derivatives and 5-methylisoxazol-3-amine which on cyclocondensation with mercaptoacetic acid afforded the desired spiro compounds.

Table 1. Chemical structures, melting points and yields of the synthesized spiro[indole-thiazolidine]dione derivatives

Entry	Structure	M.p. (˚C)	Yield (%)[a]	Entry	Structure	M.p. (˚C)	Yield (%)[a]
5a		179-181	75	***5j***		110-112	83
5b		182-184	80	***5k***		104-106	75
5c		197-199	80	***5l***		182-184	80
5d		138-140	75	***5m***		78-80	85
5e		161-163	60	***5n***		190-192	80

5f		150-152	80	***5o***		115-117	90
5g		180-182	65	***5p***		146-148	78
5h		>300	80	***5q***		195-197	80
5i		138-140	75	***5r***		197-199	80

[a]Yield of isolated products

First of all, we synthesized a category of *N*-substituted isatin based on previous reported procedures in literature (**1a-1i**) (**3**).

After that, indol-2,3-dione (**1a-1i**) was reacted with 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one or 4-amino antipyrine **2** in EtOH in the presence of 2-3 drops of acetic acid to give corresponding schiff bases as red crystalline solid in high isolated yield which on cyclocondensation with mercaptoacetic acid afforded the desired spirooxindoles. However, 4-amino antipyrine is a very reactive amine because of the neighboring effect of nitrogen in heterocyclic ring. Therefore, it works very well even in the lake of acidic catalyst. All derivatives from 4-amino antipyrine were synthesized in high yields.

To synthesis of second category of products, aniline derivatives were applied as the source of amine. Based on different aniline derivatives, yield of the reactions are different. Incorporation of fluorine often leads to changes in electronic location and rises the drug persistence by increasing the solubility in lipoid material and fat deposits in the body. Therefore, one of the selected aniline derivatives was 2,4-difluoroaniline to synthesis of **5e**, **5g** and **5i**. These three schiff bases were not separable because, the presence of two fluorine atoms on the aniline ring make it unreactive and the reaction wasn't completed. So, the next step was run directly after removing the solvent with crude intermediate without purification. Overall yields for these three products were 60%, 65% and 63% respectively. Other aniline derivatives worked well and their intermediate were completely separable through recrystallization like other entries.

To examine the versatility of this protocol, we conducted another reaction using 5-methylisoxazole-3-amine, **1b** and **1f** to synthesis of corresponding schiff bases as orange crystalline solid in high isolated yield which on cyclocondensation with mercaptoacetic acid afforded the desired spiro compounds. The results are summarized in Table 1.

Conclusion

We have elaborated a three-step synthesis of a new class of novel spiro[indoline-thiazolidine]-dione derivatives using hitherto unknown schiff bases. In these syntheses, the *N*-alkylated isatins were prepared using different alkyl halides in DMF and in the presence of potassium carbonate and tert-butyl ammonium bromide to get 1a-1i and their subsequent reaction with different amine compounds (**2a-2f**) to get schiff base intermediates (**3a-3r**). Finally, the cyclocondensation reaction of different schiff bases and mercaptoacetic acid led to the formation of the target molecules **5a–5r** in good to excellent yields.

Acknowledgements

Financial assistance from the Shiraz University of Medical Sciences by way of grant number 95-01-36-11331 is gratefully acknowledged.

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How to cite this manuscript: Masoumeh Divar*, Soghra Khabnadideh*, Razieh Sabet, Kamiar Zomorodian, Neda Ershadi, Forough Hassanpour. An Efficient Method for Synthesis of Some Novel Spiro[indoline-thiazolidine]-dione Derivatives. Chemical Methodologies 3(2), 2019, 237-250. DOI: 10.22034/chemm.2018.149025.1088.