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ORIGINAL PAPER

Synthesis of novel spirofused spiropyrrolidine 1,3-indanedione derivatives via 1,3-dipolar cycloaddition reactions

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Abstract
The successful synthesis of novel spirofused spiropyrrolidine 1,3-indanedione derivatives using 1,3-dipolar cycloaddition reactions is reported. 1-Benzyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones prepared via Knöevenagel condensation of 1-benzyl-4-piperidinone with aromatic aldehydes underwent a one-pot, three-component reaction with benzylamines and ninhydrin in ethanol to afford the desired products.

Keywords 1,3-Dipolar cycloaddition · Spirofused spiropyrrolidine 1 · 3-Indanedione · 1-Benzyl-4-piperidinone

Introduction

Multicomponent reactions (MCRs) are known as cornerstones which can be used for the synthesis of biologically interesting compounds [1–3]. These reactions, which frequently occur not through a single-step procedure, but rather by several sequential cascade or domino reactions, are powerful one-step access to products of high complexity and diversity [4, 5]. Advantages such as simplicity, high efficiency and atom economy with the preparation of complex "druglike" heterocycles in one-pot procedure can be mentioned for these reactions [6–8].

1,3-Dipolar cycloaddition is a strategic method for the construction of five-membered ring heterocycles [9–11], natural products and alkaloids [12]. Within the cycloaddition reactions, 1,3-dipolar cycloaddition of azomethine ylides with alkenes [13] is one of the most efficient and reliable strategies for the construction of functionalized five-membered pyrrolidines which exhibit antiviral [14], local anesthetic [15] and antileukemic activities [16].

On the other hand, spiro compounds represent a class of naturally occurring substances exhibiting pronounced biological properties [17, 18]. Due to the interesting biological activities of piperidine [19, 20], this substructure has been used before in the synthesis of 1-methyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones [21]. Subsequently, these derivatives were used as dipolarophiles in reaction with isatin and benzylamines [9].

Since the serendipitous discovery of ninhydrin (1,2,3-indanetriones) [**1**] by Siegfried Ruhemann in 1910, it is best known for its reactions with amino acids and amines to give the colored compounds known as Ruhemann's purple [22]. Grigg and co-worker established the intermediacy of 1,3-dipoles in the formation of Ruhemann's purple [23], since reaction of ninhydrin **1** with the α-amino acids **2** in methanol in the presence of *N*-phenylmaleimide (**4**) afforded the cycloadducts **5** stereospecifically via an *endo*-transition state involving dipoles **3** (Scheme 1a). Moreover, heating a mixture of ninhydrin (**1**), benzylamines (**6**) and *N*-methylmaleimide (**8**) in acetonitrile furnished the cycloadduct **9** stereospecifically through *endo*-transition state involving dipoles **7** (Scheme 1b) [24]. Recall that the dipole intermediates cannot be isolated since they are generated *in situ* in a solution in the presence of dipolarophiles [25].

Inspired by the known properties of spiro compounds as well as piperidine together with the importance of pyrrolidines and in continuation of our own interest in this domain [26–29], herein we report a one-pot three-component access to novel spirofused spiropyrrolidine 1,3-indanedione derivatives via 1,3-dipolar cycloaddition reaction between 1-benzyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones, benzyl amines and ninhydrin.

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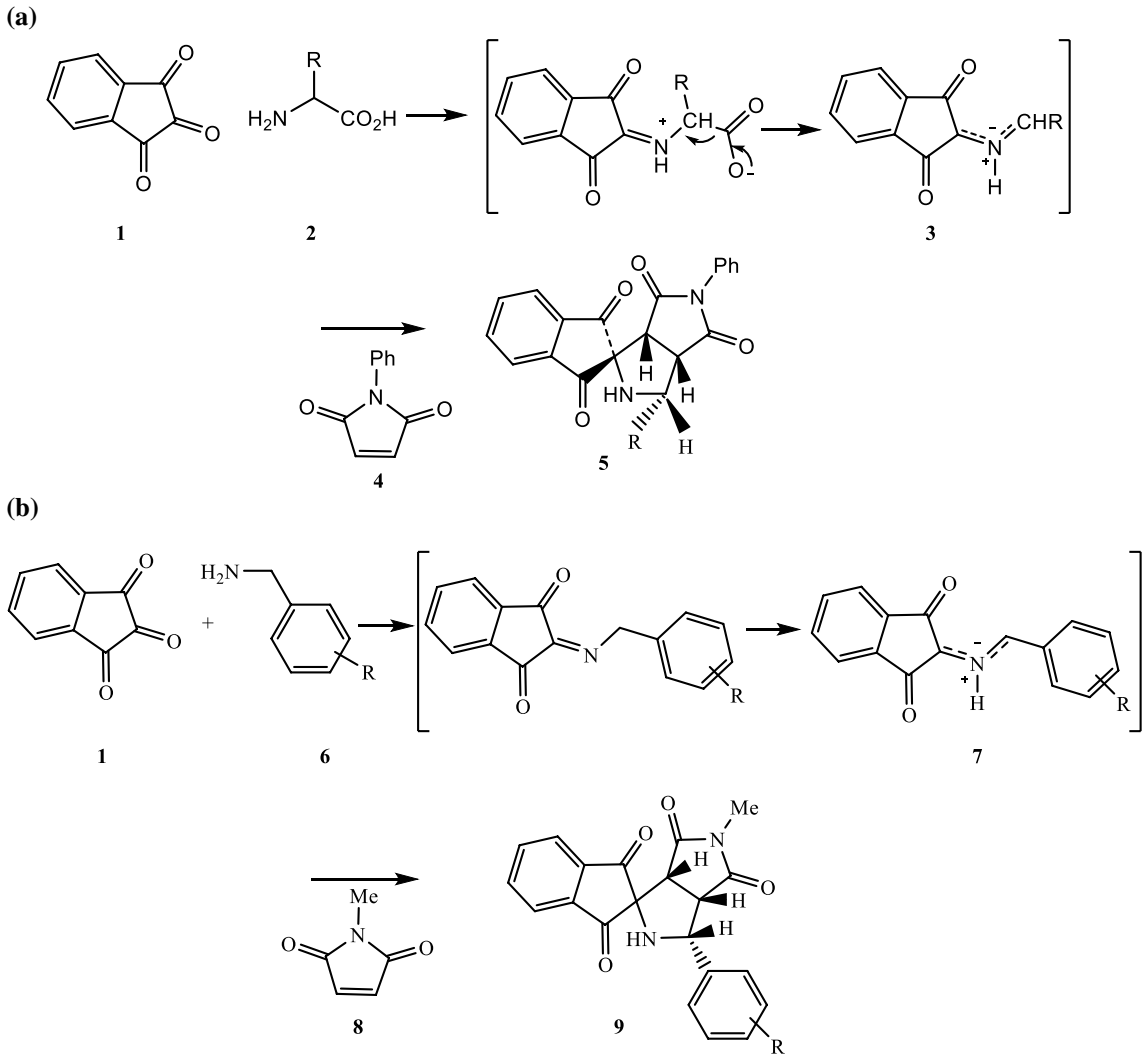


Scheme 1 Synthesis of cycloadducts **5** and **9** from ninhydrin (**1**) and the *in situ* generated azomethine ylides **3** and **7** from **a** amino acids **2** and **b** benzylamines **6**

Experimental

General information

All commercially available chemicals and reagents were purchased from Merck Chemical Company and used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and uncorrected. IR spectra were recorded on a Bomem B100 series spectrophotometer, in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300-ADVANCE spectrometer at 500 (^{1}H) and 125 MHz (^{13}C). Mass spectra of the products were obtained with an HP (Agilent Technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA).

General procedure for the preparation of 13a–i

A mixture containing ninhydrin **1** or isatin **14** (0.5 mmol), dipolarophiles **12a–e** (0.5 mmol) and benzylamines **6a–d** (0.5 mmol) in EtOH (3 mL) was stirred at reflux for 2 to 6 h. After completion as indicated by TLC, the solid was filtered, washed with EtOH and recrystallized from acetone–ethanol mixture to afford **13a–i** and **15**.

1″-Benzyl-5″-((*E*)-benzylidene)-4′,5′-diphenyldispiro[indene-2,2′-pyrrolidine-3′,3″-piperidine]-1,3,4″-trione (13a)

White solid, Yield 0.225 g (73%), mp 220–222 °C; IR (KBr) (ν_{max}, cm^{-1}) 3340 (NH), 1697(CO), 1595 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6) $\delta_H = 2.19$ (d, $J = 12.4$ Hz, 1H, –NCH), 2.80–2.83 (dd, $J = 2.8$, 15.1 Hz, 1H, –NCHPh), 3.14 (d, $J = 15.1$ Hz, 1H, –NCHPh), 3.28 (d, $J = 12.4$ Hz,

1H, –NCH), 3.61 (d, J = 12.6 Hz, 1H, –CHC=C), 3.60–3.66 (dd, J = 2.3, 12.6 Hz, 1H, –CHC=C), 3.7 (bs, 1H, –NH), 4.30 (d, J = 11.4 Hz, 1H, –CHPh), 5.30 (d, J = 11.4 Hz, 1H, –CHNH), 6.86–7.83 (m, 25H, Ar); ^{13}C NMR (125 MHz, DMSO-d_6) δ_c = 52.2, 53.6, 57.6, 60.3, 63.1, 69.7, 70.0, 122.9, 123.4, 127.5, 127.9, 128.2, 128.4, 128.5, 128.9, 129.8, 130.2, 130.3, 130.6, 132.7, 134.2, 135.9, 136.0, 136.4, 136.8, 139.5, 143.0, 143.5, 196.5, 198.0, 198.9; EI-MS m/z (%): 614 (M^+,1) 365 (86), 188 (52), 161 (69), 91(100), Anal. Calc for $C_{42}H_{34}N_2O_3$ (614.26): C 81.84, H 5.53, N 4.66%. Found: C 81.45, H 5.64, N 4.74%.

1″-Benzyl-5″-((*E*)-benzylidene)-5′-(4-fluorophenyl)-4′-phenyldispiro[indene-2,2′-pyrrolidine-3′,3″-piperidine]-1,3,4″-trione (13b)

White solid, Yield 0.175 g (55%), mp 198–200 °C; IR (KBr) (ν_{max},cm^{-1}) 3342 (NH), 1697 (CO), 1593 (C=C); ^{1}H NMR(500 MHz, DMSO-d_6) δ_H = 2.22 (d, J = 12.4 Hz, 1H, –CHN), 2.80–2.84 (dd, J = 2.7, 15.2 Hz, 1H, –NCHPh), 3.15 (d, J = 15.2 Hz, 1H, –NCHPh), 3.62–3.72 (m, 3H, –CHN, –CH_2C=C), 3.84 (d, J = 7.5 Hz, 1H, –NH), 4.35 (d, J = 11.3 Hz, 1H, –CHPh), 5.31–5.34 (dd, J = 6.65, 11.3 Hz, 1H, –CHNH), 6.84–7.84 (m, 24H, Ar); ^{13}C NMR(125 MHz, DMSO-d_6) δ_C = 30.2, 30.3, 30.4, 30.5, 30.6, 30.8, 69.7, 115.0, 116.2, 123.4, 123.5, 124.0, 127.4, 127.6, 127.9, 128.2, 128.52–128.5, 128.6, 128.8, 129.1, 129.4,130.0, 130.2,130.3, 130.6, 130.8, 135.0–136.0, 136.8, 138.1, 138.7, 142.4, 143.0, 205.6, 206.4, 207.2; EI-MS m/z (%): 632 (M^+, 1), 393 [29], 129 [30], 91 (100), 65 [12]; Anal. Calc for: $C_{42}H_{33}FN_2O_3$ (632.24): C 79.73, H 5.26, N 4.43%. Found: C 79.83, H 5.05, N 4.56%.

1″-Benzyl-5′-phenyl-4′-(pyridin-3-yl)-5″-(pyridin-3-ylmethylene)dispiro[indene-2,2′-pyrrolidine-3′,3″-piperidine]-1,3,4″-trione (13c)

White solid, Yield 0.260 g (84%), mp 218–220 °C; IR(KBr) (ν_{max}, cm^{-1}) 3336 (NH), 1698 (CO), 1595 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H = 2.19 (d, J = 12.4 Hz, 1H, –CHN), 2.91–2.94 (dd, J = 2.8, 15.2 Hz, 1H, –NCHPh), 3.11 (d, J = 15.2 Hz, 1H, –NCHPh), 3.33 (d, J = 12.4 Hz, 1H, –CHN), 3.63 (d, J = 12.8 Hz, 1H, –CHC=C), 3.76–3.87 (m, 2H, –CH C=C, NH), 4.40 (d, J = 11.4 Hz, 1H, –CHpy), 5.37 (d, J = 11.4 Hz, 1H, –CHNH), 6.85 (s, 1H, Ar), 7.19–8.44 (m, 22H, Ar); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C = 51.8, 53.2, 55.2, 60.0, 62.9, 69.4, 78.9, 122.9, 123.5, 123.7, 123.8, 127.8, 128.0, 128.1, 128.6, 130.1, 130.2, 131.5, 133.4, 134.5, 135.5, 136.0, 136.6, 137.3, 137.8, 139.1, 139.2, 143.0, 143.1, 148.9, 150.1, 151.2, 151.3, 196.2, 197.7, 198.8; EI-MS m/z (%): 616 (M^+,1), 249 (39), 233 (68), 105 (97), 77 (100), 51 (48); Anal. Calc for $C_{40}H_{32}N_4O_3$ (616.25): C 77.90, H 5.23, N 9.08%. Found: C 77.69, H 5.10, N 9.27%.

5′-(Benzo[d] [1, 3] dioxol-5-yl)-1″-benzyl-4′-(pyridin-3-yl)-5″-(pyridin-3-ylmethylene)dispiro[indene-2,2′-pyrrolidine-3′,3″-piperidine]-1,3,4″-trione (13d)

White solid, Yield 0.195 g (59%), mp 188–190 °C; IR (ν_{max}, cm^{-1}) 3340 (NH), 1699 (CO); ^{1}H NMR (500 MHz, DMSO-d_6), δ_H = 2.21 (d, J = 12.4 Hz, 1H, CHN), 2.90–2.93 (dd, J = 2.8, 15.1 Hz, 1H, –NCHPh), 3.12 (d, J = 15.1 Hz, 1H, –NCHPh), 3.32 (d, J = 12.4 Hz, 1H, –CHN), 3.64 (d, J = 12.8 Hz, 1H, –CHC=C), 3.71–3.74 (dd, J = 2.2, 12.8 Hz, 1H, –CHC=C), 3.8 (bs, 1H, –NH), 4.33 (d, J = 11.3 Hz, 1H, –CHpy), 5.31 (d, J = 11.3 Hz, 1H, –CHNH), 5.96 (d, J = 3.4 Hz, 2H, –OCH_2O), 6.76 (d, J = 7.9 Hz, 1H, Ar), 6.84 (s, 1H, Ar), 6.99–7.36 (m, 19H, Ar); ^{13}C NMR (125 MHz, DMSO-d_6), δ_C = 51.9, 53.1, 55.4, 60.1, 62.6, 69.3, 79.0, 101.3, 108.0, 121.5, 122.9, 123.5, 123.7, 123.8, 128.0, 128.6, 130.0, 130.2, 131.5, 133.4, 134.5, 135.6, 136.0, 136.6, 137.1, 137.3, 137.9, 139.2, 143.1, 147.0, 147.7, 148.8, 150.1, 151.2, 151.4, 196.2, 197.6, 199.0; EI-MS m/z (%): 660 (1, M^+), 367 [16], 339 [15], 276 (39, 91 (100); Anal. Calc for $C_{41}H_{32}N_4O_5$ (660.24): C 74.53, H 4.88, N 8.48%. Found: C 74.72, H 4.69, N 8.65%.

1″-Benzyl-5″-((*E*)-4–CHlorobenzylidene)-4′-(4–CHlorophenyl)-5′-phenyldispiro[indene-2,2′-pyrrolidine-3′,3″-piperidine]-1,3,4″-trione (13e)

White solid, Yield 0.250 g (73%), mp 217–219 °C; IR (KBr) (ν_{max}, cm^{-1}) 3342 (NH), 1697 (CO), 1593 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H = 2.18 (d, J = 12.4 Hz, 1H, –CHN), 2.84–2.87 (dd, J = 2.8, 15.0 Hz, 1H, –NCHPh), 3.12 (d, J = 15.0 Hz, 1H, –NCHPh), 3.28–3.31 (dd, J = 1.5, J = 12.4 Hz, 1H,–CHN), 3.61 (d, J = 12.6 Hz, 1H, –CHC=C), 3.67 (d, J = 12.6 Hz, 1H, –CHC=C), 3.85 (s, 1H, –NH), 4.41 (d, J = 11.2 Hz, 1H, –CHPhCl), 5.29 (d, J = 11.2 Hz, 1H, –CHNH), 6.83 (s, 1H, Ar), 6.93 (d, J = 8.1 Hz, 2H, Ar), 7.17–7.83 (m, 20H, Ar); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C = 52.0, 53.4, 56.9, 60.2, 63.2, 69.5, 78.91, 122.9, 123.4, 127.7, 128.0, 128.1, 128.5, 128.6, 128.9, 129.2, 130.2, 132.1, 132.3, 132.5, 133.1, 133.3, 134.4, 134.9, 135.4, 135.7, 136.0, 136.6, 139.3, 143.0, 143.2, 196.4, 197.8, 198.8. EI-MS m/z (%): 684 (M^+, 1), 249 (100), 220 (50), 165 (70), 89 (75); Anal. Calc for $C_{42}H_{32}Cl_2N_2O_3$ (682.18): C 73.79, H 4.72, N 4.10%. Found: C 73.52, H 4.76, N 4.21%.

1″-Benzyl-5″-((*E*)-4-chlorobenzylidene)-4′-(4-chlorophenyl)-5′-(4-fluorophenyl)dispiro[indene-2,2′-pyrrolidine-3′,3″-piperidine]-1,3,4″-trione (13f)

White solid, Yield 0.160 g (42%), mp 202–204 °C; IR (KBr) (ν_{max}, cm^{-1}) 3343 (NH), 1698 (CO), 1595 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H = 2.18 (d, J = 12.4 Hz, 1H, –CHN), 2.84–2.87 (dd, J = 2.8, 15.2 Hz, 1H, –NCHPh),

3.10 (d, $J = 15.2$ Hz, 1H, –NCHPh), 3.30 (d, $J = 12.4$ Hz, 1H, –CHN), 3.61 (d, $J = 12.7$ Hz, 1H, –CHC=C), 3.67 (dd, $J = 2.3$, 12.7 Hz, 1H, –CHC=C), 3.70 (s, 1H, –NH), 4.33 (d, $J = 11.3$ Hz, 1H, –CHPhCl), 5.31 (d, $J = 11.3$ Hz, 1H, –CHNH), 6.80 (s, 1H, CH=), 7.08–7.82 (m, 21H, Ar); ^{13}C NMR(125 MHz, DMSO-d6) $\delta_C = 56.7$, 58.1, 61.8, 65.0, 67.1, 74.2, 83.8, 119.9, 120.1, 127.7, 128.2, 132.7, 133.3, 133.6, 134.6, –134.7, 135.0, 136.9, 137.1, 137.1, 137.8, 139.2, 139.4, 138.0–140.4, 140.2, −140.8, 141.3, 144.1, 144.3, 144.3, 147.8, 165.7, 167.6, 201.1, 202.4, 203.5; IE-MS m/z (%): 701 (M^+,1), 267 (100), 238 [35], 183 (61), 146 (40), 105 (60), 76 (45); Anal. Calc for $C_{42}H_{31}Cl_2FN_2O_3$ (700.17): C 71.90, H 4.45, N 3.99%. Found: C 72.04, H 4.38, N 4.04%.

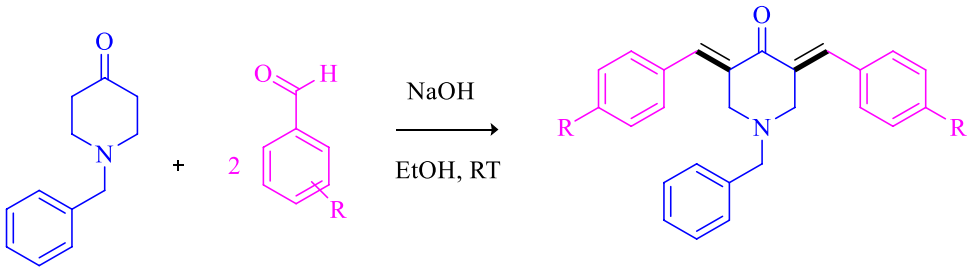
1″-Benzyl-5′-phenyl-4′-(thiophen-2-yl)-5″-(thiophen-2 ylmethylene)dispiro[indene-2,2′-pyrrolidine-3′,3″-piperidine]-1,3,4″-trione (13 g)

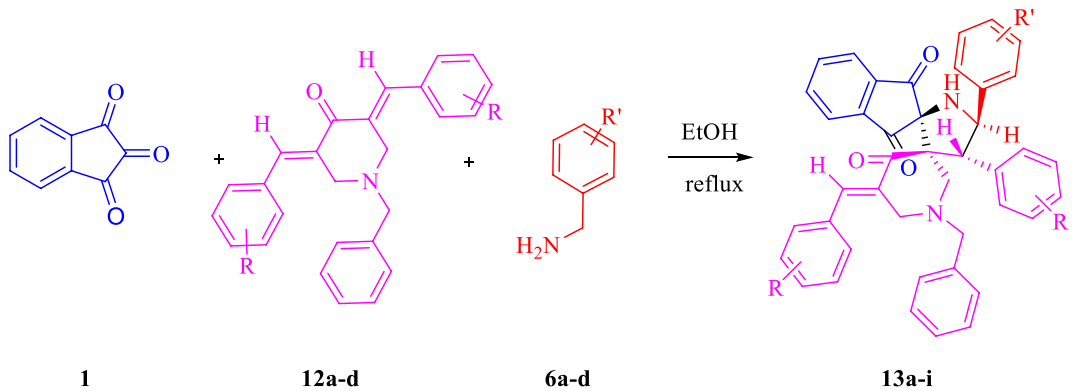
White solid, Yield: 0.26 g (83%), mp 201–203 °C; IR (KBr) (ν_{max},cm^{-1}): 3350 (NH), 1743 (CO), 1570 (C=C); ^{1}H NMR (500 MHz, DMSO-d$_6$) $\delta_H = 2.33$ (d, $J = 12.5$ Hz, 1H, –CHN), 2.79–2.83 (dd, $J = 2.7$, 15.8 Hz, 1H, NCHPh), 3.16 (d, $J = 15.8$, 1H, NCHPh), 3.34 (d, $J = 12.5$ Hz, 1H, –CHN), 3.57–3.60 (dd, $J = 2.1$, 12.6 Hz, 1H, –CHC=C), 3.69 (d, $J = 12.6$ Hz,1H, –CHC=C), 3.83 (s, 1H, –NH–), 4.65 (d, $J = 11.1$ Hz, 1H, –CHthio), 5.09 (d, $J = 11.1$ Hz,1H, –CHNH), 6.85 (s, 1H, CH=), 6.86–7.84 (m, 20H, Ar); ^{13}C NMR (125 MHz, DMSO-d$_6$) $\delta_C = 52.2$, 53.0, 53.3, 60.5, 64.6, 69.08, 79.3, 123.0, 123.4, 125.6, 127.3, 127.3, 127.8, 128.1, 128.1, 128.4, 128.5, 128.7, 128.5, 129.6,130.0, 130.3, 133.8, 135.7, 136.0, 136.5, 137.5, 138.2, 139.4, 142.7, 143.3, 195.1, 197.4, 198.7; IE-Ms m/z (%): 626 (M^+,1), 377 (68), 202 (46), 121 [33], 91 (100); Anal. Calc for $C_{38}H_{30}N_2O_3S_2$ (626.17): C 72.82, H 4.82, N 4.47; S 10.23%. Found C 72.75, H 4.74, N 4.40, S 10.19%.

1″-Benzyl-4′-(pyridin-3-yl)-5″-(pyridin-3-ylmethylene)-5′-(p -tolyl)dispiro[indene-2,2′-pyrrolidine-3′,3″-piperidine]-1,3, 4″-trione (13 h)

White solid, 0.243 g (77%), mp 208–210 °C; IR (KBr) (ν_{max}, cm^{-1}): 3342 (NH), 1695 (CO), 1595 (C=C); ^{1}H NMR (500 MHz, DMSO-d$_6$) $\delta_H = 2.15$ (d, $J = 12.4$ Hz, 1H, –CHN), 2.22 (s, 3H, Me), 2.90 (d, $J = 15.2$ Hz, 1H, –NCHPh), 3.08 (d, $J = 15.2$ Hz, 1H, –NCHPh), 3.31 (d, $J = 12.4$ Hz, 1H, –CHN), 3.60 (d, $J = 12.6$ Hz, 1H, –CHC=C), 3.73 (d, $J = 12.6$ Hz, 1H, –CHC=C), 3.85 (s, 1H, –NH), 4.34 (d, $J = 11.4$ Hz, 1H, –CHpy), 5.30 (d, $J = 11.4$ Hz, 1H, –CHNH), 6.83 (s, 1H, CH=), 7.07–8.43 (m, 21H, Ar); ^{13}C NMR (125 MHz, DMSO-d$_6$) $\delta_C = 21.1$, 53.17, 55.1, 56.3, 60.0, 62.6, 69.3, 78.7, 122.9, 123.4, 123.7, 123.8, 128.0, 128.5, 129.2, 130.1, 130.2, 131.6, 133.4, 134.5, 135.4, 136.0, 136.6, 136.9, 137.3, 137.8, 139.1, 139.8, 139.8,

Scheme 2 Synthesis of 1-benzyl-3,5-bis[(*E*)-arylmethylidene] tetrahydro-4(1*H*)-pyridinone derivative **12a–d**





Scheme 3 Synthesis of spirofused spiropyrrolidine 1,3-indanediones **13a–i**

Table 1 Synthesis of spirofused spiropyrrolidine 1,3-indanediones **13a–i**

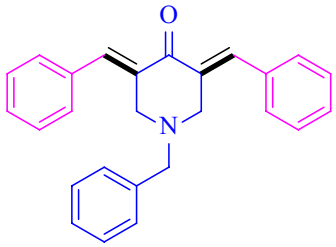
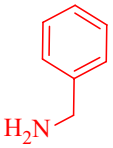
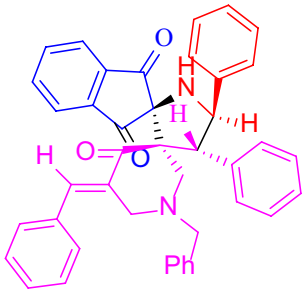
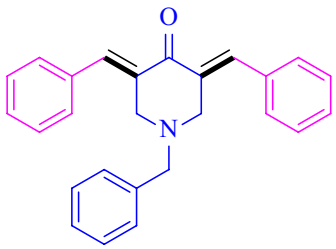
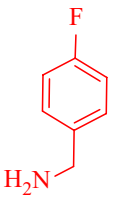
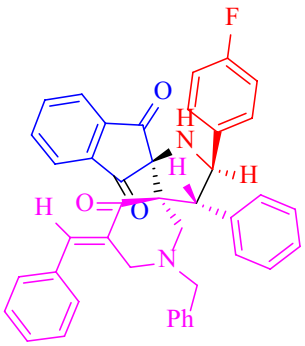
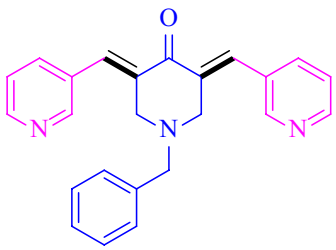
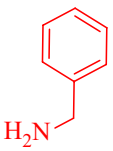
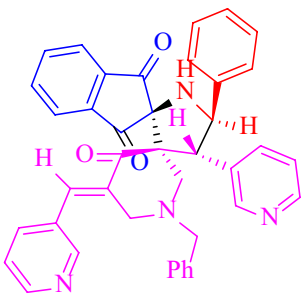
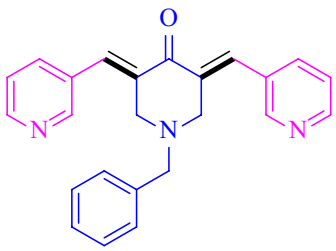
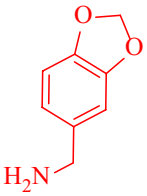
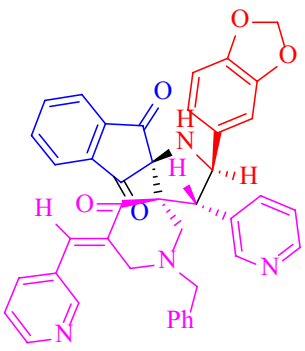
Entry	Dipolarophile	Benzylamine	Product	Yield (%)
1	 **12a**	 **6a**	 **13a**	73
2	 **12a**	 **6b**	 **13b**	55
3	 **12b**	 **6a**	 **13c**	84
4	 **12b**	 **6c**	 **13d**	59

Table 1 (continued)

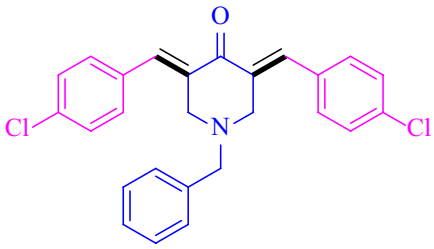
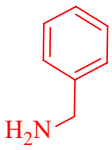
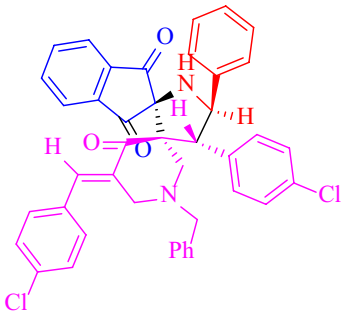
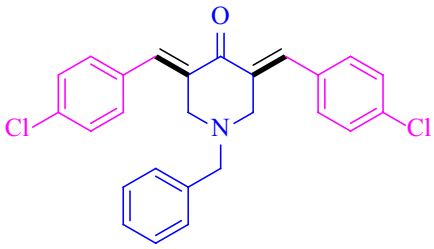
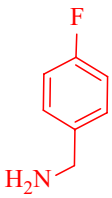
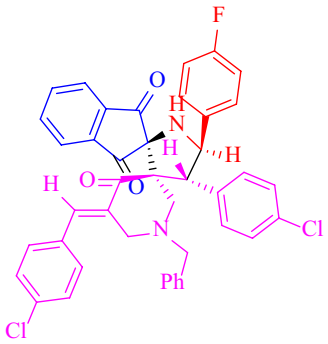
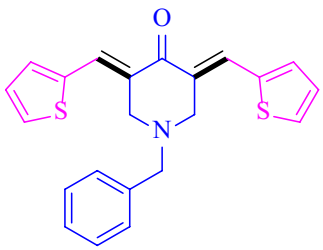
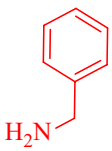
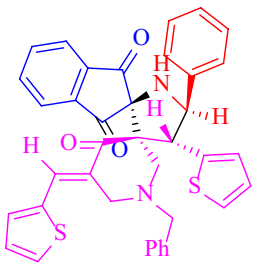
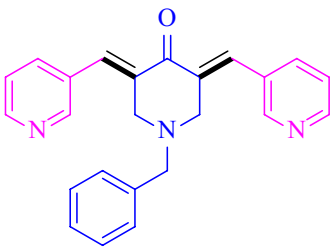
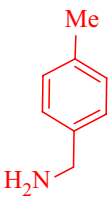
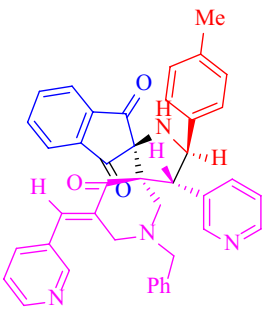
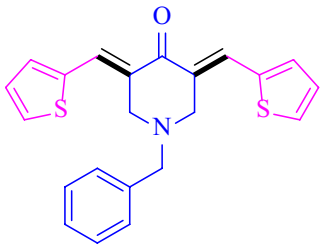
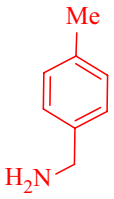
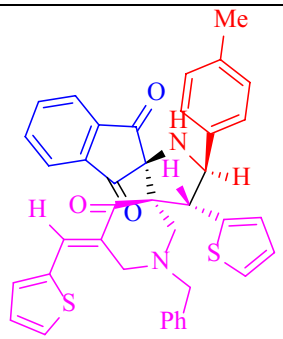
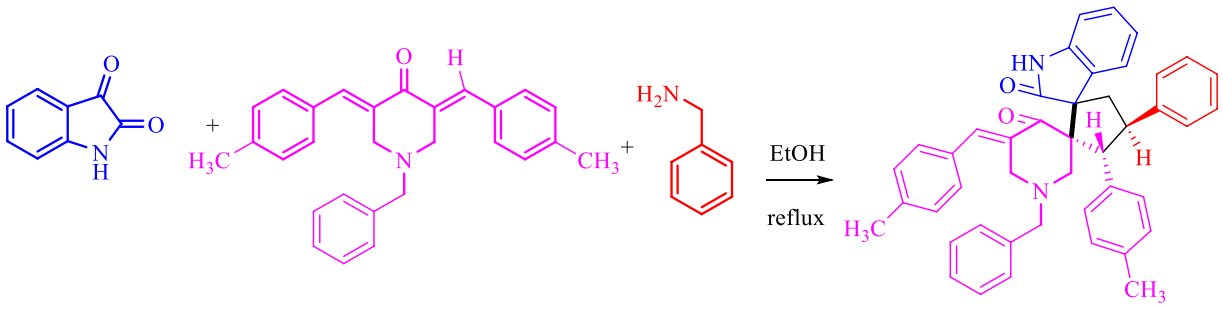
Entry	Dipolarophile	Benzylamine	Product	Yield (%)
5	 **12c**	 **6a**	 **13e**	73
6	 **12c**	 **6b**	 **13f**	55
7	 **12d**	 **6a**	 **13g**	83
8	 **12b**	 **6d**	 **13h**	77

Table 1 (continued)

Entry	Dipolarophile	Benzylamine	Product	Yield (%)
9	 **12d**	 **6d**	 **13i**	68



14 **12e** **6a** **15**

Scheme 4 Synthesis of spirofused spiropyrrolidine oxindole **15**

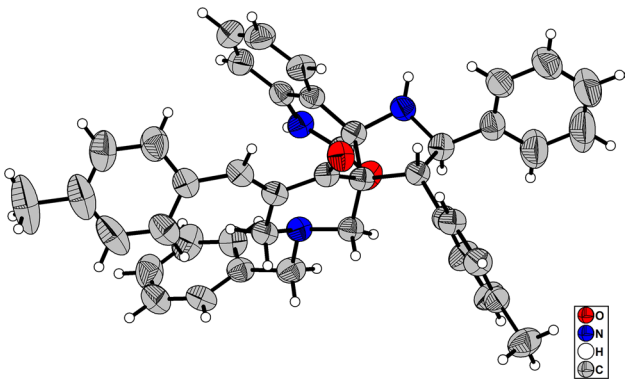
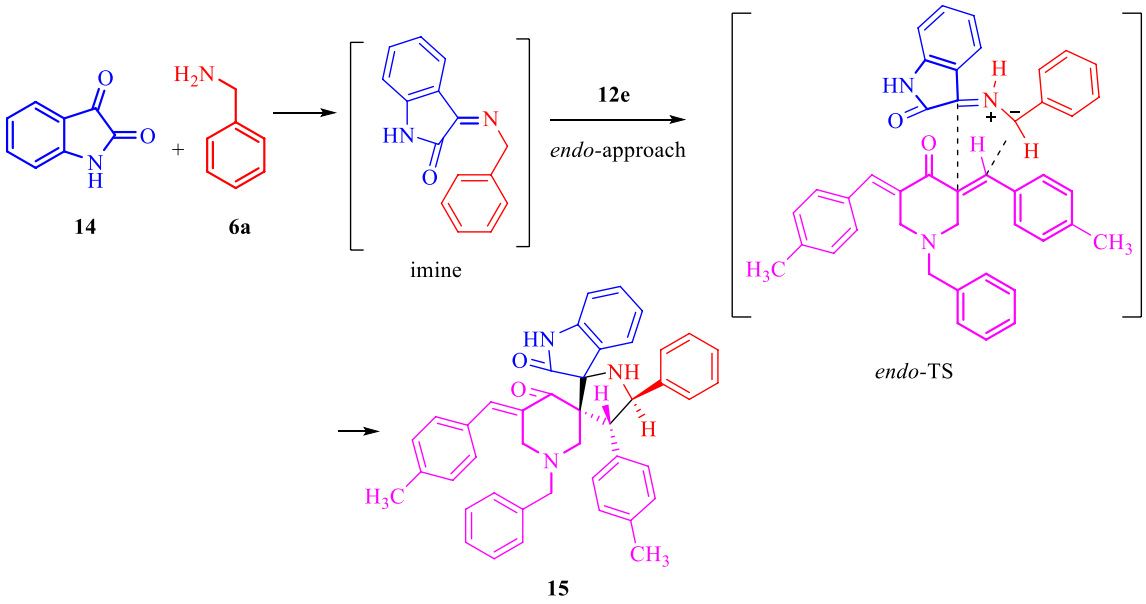


Fig. 1 ORTEP diagram of **15**

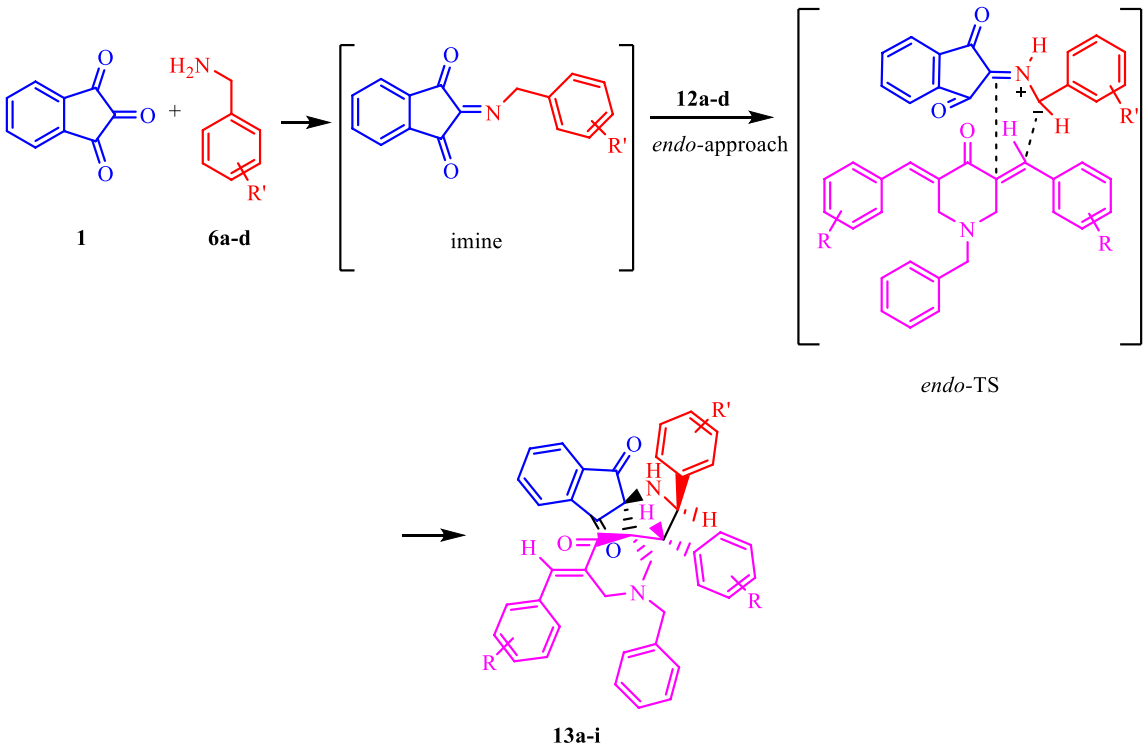
143.1, 148.8, 150.1, 151.1, 151.3, 196.3, 197.8, 198.9; IE-MS: m/z (%): 630 ($M^{+\cdot}$1), 416 [13], 366 (68), 276 (76), 91 (100); Anal. Calc for $C_{41}H_{34}N_4O_3$ (630.75): C 78.07, H 5.43, N 8.88%. Found; C 78.29, H 5.25, N 8.76%.

1″-Benzyl-4′-(thiophen-2-yl)-5″-(thiophen-2-ylmethylene)-5′-(p-tolyl)dispiro[indene-2,2′-pyrrolidine-3′,3″-piperidine]-1,3,4″-trione (13i)

White solid, Yield 0.220 g (68%), mp 202–204 °C; IR (KBr) (ν_{max}, cm^{-1}): 3345 (NH), 1740 (CO), 1508 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H = 2.10 (s, 3H, Me), 2.32 (d, J = 12.4 Hz, 1H, –CHN), 2.81 (d, J = 15.3 Hz, 1H, –NCHPh), 3.15 (d, J = 15.3 Hz, 1H, –NCHPh), 3.34 (d, J = 12.4 Hz, 1H, –CHN), 3.58 (d, J = 12.4 Hz, 1H, –CHC=C), 3.69 (d, J = 12.4 Hz, 1H, –CHC=C), 3.82 (s, 1H, –NH-), 4.61 (d, J = 11.2 Hz, 1H, –CHthio), 5.05 (d, J = 11.2 Hz, 1H, –CHNH), 6.86 (s, 1H, CH=), 6.94 (s, 1H, Ar), 7.11–7.87 (m, 18H, Ar); ^{13}C NMR (125 MHz, DMSO-d_6)δ_C = 21.2, 52.9, 53.3, 53.6, 64.4, 64.4, 69.0, 79.2, 122.9, 123.4, 125.6, 127.3, 128.1, 128.5, 128.7, 128.9, 129.1, 129.7, 130.0, 130.3, 133.8, 135.6, 135.8, 136.0, 136.5, 136.8, 136.9, 137.5, 138.2, 139.4, 140.1, 142.0, 197.5, 197.7, 198.7; IE-MS m/z (%): 640 (M^+, 1), 404 [25], 377 (77), 202 (94), 91 (100);



Scheme 5 Synthesis of spirofused spiropyrrolidine oxindole derivative **15** *via endo*-transition state



Scheme 6 Synthesis of spirofused spiropyrrolidine 1,3-indanediones derivatives **13a–i** *via endo*-transition states

Anal. Calc for $C_{39}H_{32}N_2O_3S_2$ (640.82): C 73.10, H 5.03, N 4.37, S 10.01%. Found: C 72.92, H 4.96, N 4.80, S 9.89%.

1″-Benzyl-5″-((*E*)-4-methylbenzylidene)-4′-phenyl-3′-(p-tolyl)dispiro[indoline-3,1′-cyclopentane-2′,3″-piperidine]-2,4″-dione [15]

White crystal, Yield 0.24 g (76%), mp 226–227 °C; IR (KBr) (ν_{max}, cm^{-1}): 3027 (NH), 1685 (CO), 1509 (C=C); ^1H NMR (500 MHz, DMSO-d_6), $\delta_H = 1.82$ (d, $J = 12.5$ Hz, 1H, –CHN), 2.20 (s, 3H, Me), 2.24 (s, 3H, Me), 2.74 (dd, 14.8 Hz, 1H, –NCHPh), 3.04 (d, $J = 10.6$ Hz, 1H, –CHC=C), 3.14 (d, $J = 14.8$ Hz, 1H, –NCHPh), 3.54 (m, 2H, NH, $–CH_2C=C$), 3.61 (d, $J = 12.5$ Hz, 1H, –CHN), 4.46 (d, $J = 10.3$ Hz, 1H, –CHPhMe), 5.37 (dd, $J = 6.0$, 10.3 Hz, 1H, CHNH), 6.65 (d, $J = 7.6$ Hz, 1H, Ar), 6.80–6.90 (m, 3H, Ar), 6.92–7.27 (m, 13H, Ar), 7.48 (d, $J = 6.9$ Hz, 2H, Ar), 10.44 (s, 1H, –NHCO); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta_C = 21.1$, 21.3, 53.9, 57.3, 57.8, 62.4, 63.5, 65.1, 71.7, 109.1, 120.9, 127.3, 127.4, 127.6, 128.0, 128.4, 128.5, 128.7, 129.3, 129.4, 129.4, 129.6, 130.0, 130.4, 132.2, 132.6, 135.2, 136.1, 137.0, 137.4, 139.3, 142.8, 143.3, 180.2, 199.0; IE-MS m/z (%): 629 (1, M^+), 393 [25], 365 [10], 207 [17], 115 [28], 133 (63), 91 (100); Anal. Calcd for $C_{43}H_{39}N_3O_2$ (629.30): C 82.01, H 6.24, N 6.67%. Found: C 81.55, H 6.47, N 6.84%.

Results and discussion

Initially, 1-benzyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinone derivatives **12a–d** were prepared via Knöevenagel condensation of 1-benzyl-4-piperidinone **10** with aromatic aldehydes **11a–d** using the previously reported procedure [21] (Scheme 2). In the next step, a mixture of ninhydrin **1** and benzylamines **6a–d** was stirred at room temperature for 10 min. After the formation of the corresponding imines as indicated by change in color from yellow to light violet, derivatives **12a–d** were added and the deep violet solutions heated at reflux for appropriate times. Upon completion as indicated by TLC, the solids were separated and washed with cold EtOH. Recrystallization of solids from a mixture of acetone and EtOH finally afforded the desired products **13a–i** in satisfactory yields (Scheme 3, Table 1). All compounds were characterized by elemental analysis, MS, IR, and ^1H and ^{13}C NMR spectroscopy. The stereochemistry of **13a–i** was apparent on the basis of ^1H NMR spectra in which benzylic protons of pyrrolidine rings appear as two doublets with $J = 11.1$ to 11.4 Hz, indicating a *trans* stereochemistry. Since no X-ray crystallography could be obtained for **13a–i**, isatin **14** was used to study its reaction with **12e** and benzylamine (**6a**). As shown in Scheme 4, the product **15** is formed with high regio- and stereoselectivity with vicinal *trans* benzylic protons confirmed by using monocrystal X-ray diffraction analysis (Fig. 1) [30]. The regioselectivity observed in **15** can be attributed to the regioselective *endo*-approach of the dipole toward the termini of the dipolarophile **12e** (Scheme 5).

Since the *trans* benzylic protons of **13a–i** appear as a doublet with large coupling constants between $J = 11.1$ to 11.4 Hz, the formation of spirofused spiropyrrolidine 1,3-indanediones **13a–i** via the *endo*-transition states of the dipole toward the termini of the dipolarophiles **12a–d** with vicinal *trans* benzylic protons is concluded (Scheme 6).

These cycloadditions are chemoselective since addition occurs exclusively on one double bond of **12a–d**, affording the mono-spiropyrrolidine 1,3-indanedione derivatives, perhaps due to the steric effect experienced on the *in situ* generated azomethine ylides by **13a–i** on the second cycloaddition to bis-spiropyrrolidine 1,3-indanediones. Moreover, these cycloadditions also proceed stereoselectively since in all cases only one diastereomer with four stereocenters is obtained in satisfactory yields (55–84%).

Conclusion

In conclusion, a number of spirofused spiropyrrolidine 1,3-indanediones were synthesized via a three-component reaction of 1-benzyl-3,5-bis[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones **12a–d** with benzyl amines **6a–d** and ninhydrin [**1**]. These new structures broaden the hybrid scaffolds that are accessible through a one-pot reaction, and many of them may represent interesting pharmacophores.

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References

1. B. Liang, S. Kalidindi, J.R. Porco Jr., C.R. Stephenson, Org. Lett. **12**, 572 (2010)
2. S.L. Cui, X.F. Lin, Y.G. Wang, Org. Lett. **8**, 4517 (2006)
3. B. Ganem, Acc. Chem. Res. **42**, 463 (2009)
4. K. Kriis, K. Ausmees, T. Pehk, M. Lopp, T. Kanger, Org. Lett. **12**, 2230 (2010)
5. J.D. Sunderhaus, S.F. Martin, Chem. Eur. J. **15**, 1300 (2009)
6. L. Banfi, R. Riva, Org. Reaction **65**, 1 (2005)
7. D.J. Ramón, M. Yus, Angew. Chem. Int. Ed. **44**, 1602 (2005)
8. A. Dömling, Chem. Rev. **106**, 17 (2006)
9. R.R. Kumar, S. Perumal, Tetrahedron **63**, 12220 (2007)
10. M.S. Singh, S. Chowdhury, S. Koley, Tetrahedron **72**, 1603 (2016)
11. A.A. Raj, R. Raghunathan, Tetrahedron **57**, 10293 (2001)
12. V. Jager, R. Muller, T. Liebold, M. Hein, M. Schwarz, M. Fengler, L. Jaroskova, M. Patzel, P.Y. Le Roy, P. Bull. Soc. Chim. Belg. **103**, 491 (1994)

13. I. Coldham, R. Hufton, Chem. Rev. **15**, 2765 (2005)
14. N. Uchide, K. Ohyama, J. Antimicrob. Chemother. **52**, 8 (2003)
15. M.J. Kornett, A.P. Thio, J. Med. Chem. **19**, 892 (1976)
16. M.A. Abou-Gharbia, P.H. Doukas, Heterocycles **12**, 637 (1979)
17. J. Kobayashi, M. Tsuda, K. Agemi, H. Shigemori, M. Ishibashi, T. Sasaki, Y. Mikami, Tetrahedron **47**, 6617 (1991)
18. D.M. James, H.B. Kunze, D.J.J. Faulkner, D. Nat, Prod. **54**, 1137 (1991)
19. E. Abignente, M. Biniecka-Picazio, M. Acta Pol. Pharm. **34**, 241 (1977)
20. J.R. Dimmock, J.A. Jha, G.A. Zello, G.R.K. Sharma, A. Shrivastav, P. Selvakumar, T.M. Allen, C.L. Santos, J. Balzarini, E. De Clercq, E.K. Manavathu, J.P.J. Stables, Enzyme Inhib. Med. Chem. **18**, 325 (2003)
21. Z.G. Han, S.J. Tu, B. Jiang, S. Yan, X.H. Zhang, S.S. Wu, W.J. Hao, X.D. Cao, F. Shi, G. Zhang, N. Ma, Synthesis, 1639 (2009)
22. S. Ruhemann, J. Chem. Soc. **97**, 1438 (1910)
23. R. Grigg, S. Thianpatanagul, J. Chem. Soc. Chem. Commun. 180 (1984)
24. H. Ardill, M.J.R. Dorrity, R. Grigg, Tetrahedron **46**, 6433 (1990)
25. A.S. Filatov, S. Wang, O.V. Khoroshilova, S.V. Lozovskiy, A.G. Larina, V.M. Boitsov, A.V. Stepakov, J. Org. Chem. **84**, 7017 (2019)
26. M. Ghandi, A. Yari, S.J. Tabatabaei Rezaei, A. Taheri, Tetrahedron Lett. **50**, 4724 (2009)
27. M. Ghandi, A. Taheri, A. Abbasi, Tetrahedron **66**, 6744 (2010)
28. M. Ghandi, A. Taheri, A. Hasani Bozcheloei, A. Abbasi, R. Kia, Tetrahedron **68**, 3641 (2012)
29. M. Ghandi, N. Zarezadeh, A. Abbasi, RSC Adv. **6**, 67805 (2016)
30. Crystallographic data for **6a** has been deposited in the Cambridge Crystallographic Data Centre with the deposition numbers CCDC 1953641. http://www.ccdc.ca-m.ac.uk/conts/retrieving.html