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Chemoselective cyclization of 3-arylamino-2-hydroxy-tetrahydroindol-4-one in water at room temperature

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Abstract

A convenient and green protocol is developed for the chemoselective synthesis of indole derivatives by the one-pot, multi-component reaction of 5,5-dimethyl-3-(arylamino)cyclohex-2-enone derivatives (derived from the addition of various anilines to dimedone) with phenylglyoxal monohydrate, and diverse anilines, in water at room temperature. Advantages of this reaction include the availability of starting materials, use of water as a green solvent, catalyst-free approach, simple work-up, high yields, and preparation of potentially bioactive compounds.

Keyword: Organic chemistry

1. Introduction

The indole moiety is probably the most well-known heterocycle, which occurs in many important natural products, pharmaceuticals, and other synthetic materials [1]. Indole derivatives have received considerable attention during the past years due to their wide range of biological activities such as anti-inflammatory, analgesic, antipyretic [2], anticancer [3], anti-HIV [4], antifungal [5], antiviral [6], antibacterial,

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anticonvulsant, and cardiovascular [7] activities. Structures of some naturally occurring indoles (tryptophan, serotonin, and melatonin) are designated in Fig. 1 [8]. During recent years, many researchers have described synthesis of indole and its derivatives along with its applications in the literature [9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20]. For example in 2017 Hao et al. reported a new and highly eco-friendly approach to diverse and functionalized oxazolo [5,4-b] indoles with good yield and high diastereoselectivity by the reaction of arylglyoxals, cyclic enaminones, and amino acids in EtOH as a solvent under microwave irradiation conditions at 80 °C [21].

Choice of solvent is one of the problems to face in order to perform eco-efficient processes [22]. Water is considered as a benign solvent in comparison to the conventional organic solvents because of its practical advantages such as easy availability, cheap, abundance, non-inflammable, non-explosivity, and non-toxic [23]. Water is not simply an environmentally benign solvent; it has special properties that are essentially unique, related to what is called the "hydrophobic effect" [24]. In the 1980s Breslow showed that hydrophobic effects can strongly enhance the rate of several organic reactions [22].

Also multi-component reaction (MCR) chemistry is a technique that allows for efficient and diverse access to multiple bioactive scaffolds [25]. MCRs are of great relevance to green chemistry because they minimize the waste generation and afford high yields by reducing number of steps as compared to multistep synthesis [26]. Hence the main objective of the present study was to design new and versatile MCR synthesis of novel indole derivatives *via* the one-pot, multi-component reaction of dimedone, phenylglyoxal monohydrate, and various anilines in water at room temperature without the use of any catalyst.

2. Experimental

2.1. Reagent and apparatus

The dimedone, phenylglyoxal monohydrate, various anilines and other chemicals and solvents were obtained from Merck and Aldrich and were used without further purification. NMR spectra were recorded with a Bruker DRX-300 Avance instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) with DMSO and $CDCl_3$ as solvent. Chemical shifts are given in ppm (δ), and coupling constant (J) are reported in hertz (Hz). Melting

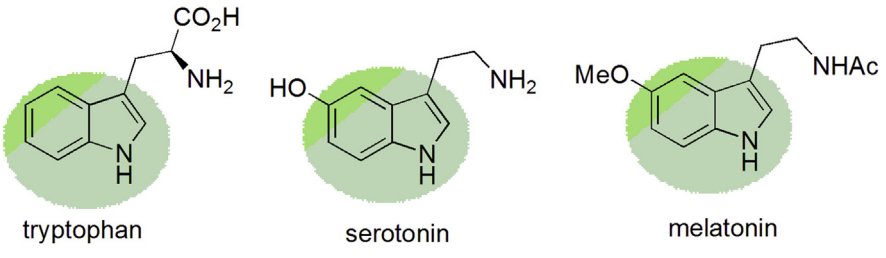

Fig. 1. Selected examples of naturally occurring indole skeleton.

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points were measured with an electrothermal 9100 apparatus. Mass spectra were recorded with an Agilent 5975C VL MSD with Triple-Axis Detector operating at an ionization potential of 70 eV. IR spectra were measured with, Bruker Tensor 27 spectrometer.

2.2. General procedure for the synthesis of product 6a

A mixture of dimedone **1** (1 mmol, 0.140 g) and 4-chloroaniline **2** (1 mmol, 0.127 g) were melted at 80 °C for 15 min. Then water (5 mL), phenylglyoxal monohydrate **4** (1 mmol, 0.152 g), 4-chloroaniline **5** (1 mmol, 0.127 g) were added and the solution was stirred at room temperature for 5 hours. Upon completion as monitored by TLC (ethyl acetate/n-hexane, 1:1), the precipitates were filtered and washed with water to give product **6a** in 95% yield.

2.3. Spectral data

2.3.1. 3-(4-chlorophenylamino)-1-(4-chlorophenyl)-2,3,6,7-tetrahydro-2-hydroxy-6,6-dimethyl-2-phenyl-1H-indol-4(5H)-one (6a)

White powder, mp: 199−201 °C, 0.468 g, yield: 95%. IR (KBr) (ν_{max}/cm^{-1}): 3372, 3315 (OH, NH), 2949 (CH), 1602 (C=O), 1557 (Ar), 1280 (C-N). MS (EI, 70 eV): *m/z* (%) = 365 (58), 336 (62), 260 (24), 127 (100), 105 (37), 77 (25). ^{1}H NMR (300 MHz, DMSO-d_6): Major diastereomer (56%): δ 1.04 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.01−2.25 (4H, m, $2CH_2$), 4.32 (1H, d, $^{3}J_{HH}$ = 6.0 Hz, CH), 5.62 (1H, d, $^{3}J_{HH}$ = 6.0 Hz, NH), 6.15−7.45 (13H, m, Ar), 6.51 (1H, s, OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 28.3 (CH_3), 29.1 (CH_3), 34.1 ($C(CH_3)_2$), 37.6 (CH_2), 51.0 (CH_2), 64.8 (CH), 96.9 (C-OH), 107.2, 115.2, 120.4, 125.2, 127.9, 128.6, 129.0, 129.6, 131.4, 136.3, 137.7, 143.3, 148.0, 164.8, 190.3 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): Minor diastereomer (44%): δ 1.01 (3H, s, CH_3), 1.13 (3H, s, CH_3), 2.30−2.62 (4H, m, $2CH_2$), 4.54 (1H, d, $^{3}J_{HH}$ = 7.2 Hz, CH), 5.69 (1H, d, $^{3}J_{HH}$ = 7.2 Hz, NH), 6.15−7.45 (14H, m, Ar and OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 27.8 (CH_3), 29.8 (CH_3), 34.6 ($C(CH_3)_2$), 38.0 (CH_2), 51.4 (CH_2), 65.4 (CH), 100.0 (C-OH), 108.5, 113.7, 118.5, 126.7, 127.6, 128.3, 128.7, 129.4, 130.5, 137.1, 137.5, 146.2 146.9, 164.6, 190.8 (C=O).

2.3.2. 3-(3,4-dichlorophenylamino)-1-(4-bromophenyl)-2,3,6,7-tetrahydro-2-hydroxy-6,6-dimethyl-2-phenyl-1H-indol-4(5H)-one (6b)

White powder, mp: 194−196 °C, 0.497 g, yield: 87%. IR (KBr) (ν_{max}/cm^{-1}): 3387−3313 (OH, NH), 2953 (CH), 1601 (C=O), 1559 (Ar), 1279 (C-N). ^{1}H

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NMR (300 MHz, DMSO-d_6): Major diastereomer (100%): δ 1.04 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.05−2.25 (4H, m, $2CH_2$), 4.30 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 5.91 (1H, d, $^3J_{HH}$ = 6.0 Hz, NH), 6.39−7.50 (12H, m, Ar), 6.77 (1H, s, OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 28.3 (CH_3), 29.1 (CH_3), 34.1 ($C(CH_3)_2$), 37.5 (CH_2), 51.0 (CH_2), 64.5 (CH), 97.1 (C-OH), 107.0, 114.0, 114.6, 119.0, 125.2, 128.6, 129.0, 129.8, 130.4, 130.8, 131.2, 132.0, 136.6, 143.2, 149.3, 164.8, 190.3 (C=O).

2.3.3. 3-(3,4-dichlorophenylamino)-1-(4-chlorophenyl)-2,3,6,7-tetrahydro-2-hydroxy-6,6-dimethyl-2-phenyl-1H-indol-4(5H)-one (6c)

White powder, mp: 195−197 °C, 0.401 g, yield: 76%. ^{1}H NMR (300 MHz, DMSO-d_6): Major diastereomer (52%): δ 1.04 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.02−2.24 (4H, m, $2CH_2$), 4.32 (1H, d, $^3J_{HH}$ = 5.7 Hz, CH), 5.90 (1H, d, $^3J_{HH}$ = 6.3 Hz, NH), 6.23−7.45 (12H, m, Ar), 6.75 (1H, s, OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 28.3 (CH_3), 29.1 (CH_3), 34.1 ($C(CH_3)_2$), 37.6 (CH_2), 51.0 (CH_2), 65.1 (CH), 97.1 (C-OH), 106.9, 114.0, 114.5, 115.8, 125.2, 128.6, 128.9, 129.5, 130.5, 131.5, 136.1, 137.5, 143.4, 149.3, 149.4, 164.9, 191.0 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): Minor diastereomer (48%): δ 1.00 (3H, s, CH_3), 1.13 (3H, s, CH_3), 2.29−2.62 (4H, m, $2CH_2$), 4.53 (1H, d, $^3J_{HH}$ = 6.9 Hz, CH), 6.02 (1H, d, $^3J_{HH}$ = 6.9 Hz, NH), 6.23−7.45 (13H, m, Ar and OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 27.8 (CH_3), 29.6 (CH_3), 34.7 ($C(CH_3)_2$), 38.0 (CH_2), 51.4 (CH_2), 64.6 (CH), 99.8 (C-OH), 108.5, 112.3, 112.7, 113.7, 126.8, 128.7, 129.0, 129.8, 130.4, 131.1, 137.0, 139.0, 143.1, 148.0, 152.0, 165.3, 190.3 (C=O).

2.3.4. 3-(4-bromophenylamino)-1-(4-chlorophenyl)-2,3,6,7-tetrahydro-2-hydroxy-6,6-dimethyl-2-phenyl-1H-indol-4(5H)-one (6d)

White powder, mp: 192−194 °C, 0.446 g, yield: 83%. ^{1}H NMR (300 MHz, DMSO-d_6): Major diastereomer (89%): δ 1.04 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.08−2.24 (4H, m, $2CH_2$), 4.32 (1H, d, $^3J_{HH}$ = 6.0 Hz, CH), 5.62 (1H, d, $^3J_{HH}$ = 6.3 Hz, NH), 6.33−7.50 (13H, m, Ar), 6.59 (1H, s, OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 28.4 (CH_3), 29.0 (CH_3), 34.2 ($C(CH_3)_2$), 37.6 (CH_2), 51.1 (CH_2), 64.6 (CH), 96.9 (C-OH), 107.2, 107.7, 115.2, 115.7, 125.2, 128.5, 129.0, 129.0, 129.4, 131.4, 136.3, 143.3, 148.4, 164.9, 190.4 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): Minor diastereomer (11%): δ 1.00 (3H, s, CH_3), 1.13 (3H, s, CH_3), 2.30−2.62 (4H, m, $2CH_2$), 4.54 (1H, d, $^3J_{HH}$ = 7.2 Hz, CH), 5.69 (1H, d, $^3J_{HH}$ = 7.2 Hz, NH), 6.33−7.50 (14H, m, Ar and OH).

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2.3.5. 3-(3,4-dichlorophenylamino)-2,3,6,7-tetrahydro-2-hydroxy-6,6-dimethyl-1-(3,5-dimethylphenyl)-2-phenyl-1H-indol-4(5H)-one (6e)

White powder, mp: 170−172 °C, 0.417 g, yield: 80%. ^{1}H NMR (300 MHz, DMSO-d_6): Major diastereomer (100%): δ 1.02 (3H, s, CH_3), 1.06 (3H, s, CH_3), 2.05−2.23 (4H, m, $2CH_2$), 2.10 (6H, s, $2CH_3$), 4.65 (1H, d, CH), 5.85 (1H, d, NH), 6.31−7.50 (11H, m, Ar), 6.79 (1H, s, OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 19.0 (CH_3), 22.0 (CH_3), 28.4 (CH_3), 29.1 (CH_3), 34.0 ($C(CH_3)_2$), 37.7 (CH_2), 51.1 (CH_2), 64.6 (CH), 97.0 (C-OH), 107.2, 114.0 114.7, 117.4, 123.7, 125.2, 126.0, 126.6, 127.6, 128.0, 130.4, 131.1, 137.9, 143.6, 149.3, 165.6, 189.9 (C=O). MS (EI, 70 eV): *m/z* (%) = 519 (M^+-2, 6), 359 (100), 343 (26), 303 (18), 254 (27), 127 (7), 105 (22), 77 (17).

2.3.6. 3-(4-chlorophenylamino)-1-(4-bromophenyl)-2,3,6,7-tetrahydro-2-hydroxy-6,6-dimethyl-2-phenyl-1H-indol-4(5H)-one (6f)

White powder, mp: 177−179 °C, 0.430 g, yield: 80%. MS (EI, 70 eV): *m/z* (%) = 536 (M^+-2, 7), 365 (100), 349 (32), 308 (29), 217 (8), 127 (13), 105 (11), 77 (9). ^{1}H NMR (300 MHz, DMSO-d_6): Major diastereomer (90%): δ 1.04 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.05−2.22 (4H, m, $2CH_2$), 4.32 (1H, d, $^{3}J_{HH}$ = 6.0 Hz, CH), 5.60 (1H, d, $^{3}J_{HH}$ = 6.3 Hz, NH), 6.33−7.50 (13H, m, Ar), 6.58 (1H, s, OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 28.4 (CH_3), 29.0 (CH_3), 34.2 ($C(CH_3)_2$), 37.6 (CH_2), 51.1 (CH_2), 64.8 (CH), 96.9 (C-OH), 106.0, 107.3, 115.2, 119.7, 120.4, 125.2, 128.6, 129.0, 129.6, 132.0, 136.7, 143.3, 148.0, 164.8, 190.4 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): Minor diastereomer (10%): δ 1.00 (3H, s, CH_3), 1.13 (3H, s, CH_3), 2.23−2.60 (4H, m, $2CH_2$), 4.55 (1H, d, $^{3}J_{HH}$ = 7.2 Hz, CH), 5.65 (1H, d, $^{3}J_{HH}$ = 7.2 Hz, NH), 6.33−7.50 (14H, m, Ar and OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 27.8 (CH_3), 29.6 (CH_3), 34.7 ($C(CH_3)_2$), 37.9 (CH_2), 51.4 (CH_2), 65.0 (CH), 99.9 (C-OH), 105.7, 108.6, 113.7, 118.5, 118.9, 126.7, 127.6, 127.9, 128.3, 131.4, 137.6, 141.0, 146.8, 164.5, 190.8 (C=O).

2.3.7. 3-(3,4-dichlorophenylamino)-2,3,6,7-tetrahydro-2-hydroxy-6,6-dimethyl-1,2-diphenyl-1H-indol-4(5H)-one (6g)

White powder, mp: 190−192 °C, 0.399 g, yield: 81%. ^{1}H NMR (300 MHz, DMSO-d_6): Major diastereomer (64%): δ 1.04 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.03−2.22 (4H, m, $2CH_2$), 4.31 (1H, d, $^{3}J_{HH}$ = 6.3 Hz, CH), 5.90 (1H, d, $^{3}J_{HH}$ = 6.3 Hz, NH), 6.23−7.50 (13H, m, Ar), 6.66 (1H, s, OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 28.3 (CH_3), 29.1 (CH_3), 34.1 ($C(CH_3)_2$), 37.6 (CH_2), 51.1 (CH_2), 64.6 (CH), 97.0 (C-OH), 106.3, 112.8, 114.1, 115.8, 125.2, 126.7, 127.6,

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128.1, 128.5, 129.8, 130.5, 131.1, 137.1, 143.5, 149.1, 164.9, 191.0 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): Minor diastereomer (36%): δ 1.00 (3H, s, CH_3), 1.13 (3H, s, CH_3), 2.28−2.57 (4H, m, $2CH_2$), 4.54 (1H, d, $^{3}J_{HH}$ = 6.9 Hz, CH), 6.02 (1H, d, $^{3}J_{HH}$ = 7.2 Hz, NH), 6.23−7.50 (14H, m, Ar and OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 27.8 (CH_3), 29.6 (CH_3), 34.7 ($C(CH_3)_2$), 38.0 (CH_2), 51.4 (CH_2), 65.3 (CH), 99.9 (C-OH), 107.6, 113.2, 114.7, 117.4, 126.2, 127.1, 127.4, 127.9, 128.4, 129.7, 130.4, 130.6, 137.9, 147.5, 148.0, 164.9, 190.3 (C=O).

2.3.8. 3-(4-bromophenylamino)-2,3,6,7-tetrahydro-2-hydroxy-6,6-dimethyl-1,2-diphenyl-1H-indol-4(5H)-one (6h)

White powder, mp: 177−179 °C, 0.427 g, yield: 85%. ^{1}H NMR (300 MHz, DMSO-d_6): Major diastereomer (67%): δ 1.03 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.05−2.21 (4H, m, $2CH_2$), 4.31 (1H, d, CH), 5.61 (1H, d, NH), 6.21−7.47 (14H, m, Ar), 6.49 (1H, s, OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 28.3 (CH_3), 29.1 (CH_3), 34.1 ($C(CH_3)_2$), 37.7 (CH_2), 51.1 (CH_2), 64.8 (CH), 96.8 (C-OH), 106.7, 115.8, 125.2, 126.6, 127.4, 127.9, 128.4, 128.9, 128.9, 131.4, 137.2, 143.6, 148.4, 164.9, 190.1 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): Minor diastereomer (33%): δ 1.00 (3H, s, CH_3), 1.12 (3H, s, CH_3), 2.28−2.60 (4H, m, $2CH_2$), 4.53 (1H, d, CH), 5.69 (1H, d, NH), 6.21−7.47 (15H, m, Ar and OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 27.8 (CH_3), 29.6 (CH_3), 34.6 ($C(CH_3)_2$), 38.1 (CH_2), 51.4 (CH_2), 65.5 (CH), 99.9 (C-OH), 107.9, 114.3, 126.0, 126.4, 126.8, 127.0, 128.2, 129.1, 131.6, 130.7, 138.0, 147.0, 147.8, 164.9, 191.0 (C=O).

2.3.9. 3-(4-bromophenylamino)-1-(3,4-dichlorophenyl)-2,3,6,7-tetrahydro-2-hydroxy-6,6-dimethyl-2-phenyl-1H-indol-4(5H)-one (6i)

White powder, mp: 169−171 °C, 0.389 g, yield: 68%. ^{1}H NMR (300 MHz, DMSO-d_6): Major diastereomer (57%): δ 1.04 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.06−2.24 (4H, m, $2CH_2$), 4.30 (1H, d, $^{3}J_{HH}$ = 5.7 Hz, CH), 5.64 (1H, d, $^{3}J_{HH}$ = 6.0 Hz, NH), 6.19−7.50 (12H, m, Ar), 6.70 (1H, s, OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 28.2 (CH_3), 29.1 (CH_3), 34.2 ($C(CH_3)_2$), 37.6 (CH_2), 51.0 (CH_2), 65.1 (CH), 97.1 (C-OH), 106.0, 107.9, 109.0, 115.7, 122.0, 125.2, 127.7, 128.4, 129.1, 130.8, 131.2, 137.5, 143.4, 148.4, 160.0, 164.9, 190.7 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): Minor diastereomer (43%): δ 1.00 (3H, s, CH_3), 1.13 (3H, s, CH_3), 2.26−2.66 (4H, m, $2CH_2$), 4.53 (1H, d, CH), 5.72 (1H, d, NH), 6.19−7.50 (13H, m, Ar and OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 27.6 (CH_3), 29.8 (CH_3), 34.9 ($C(CH_3)_2$), 38.0 (CH_2), 51.4 (CH_2), 64.6 (CH), 100.0 (C-OH), 107.8, 108.5, 110.5, 114.3, 123.9, 126.9, 128.2, 128.6, 129.2, 131.4, 131.6, 138.4, 146.0, 147.0, 155.0, 164.9, 191.5 (C=O).

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2.3.10. 3-(4-chlorophenylamino)-1-(3,4-dichlorophenyl)-2,3,6,7-tetrahydro-2-hydroxy-6,6-dimethyl-2-phenyl-1H-indol-4(5H)-one (6j)

White powder, mp: 169−171 °C, 0.469 g, yield: 89%. MS (EI, 70 eV): *m/z* (%) = 525 (M^+-2, 10), 399 (100), 383 (31), 342 (30), 296 (33), 127 (69), 105 (38), 77 (31). ^{1}H NMR (300 MHz, DMSO-d_6): Major diastereomer (55%): δ 1.04 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.01−2.22 (4H, m, $2CH_2$), 4.30 (1H, d, CH), 5.62 (1H, d, NH), 6.25−7.50 (12H, m, Ar), 6.70 (1H, s, OH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 28.8 (CH_3), 29.2 (CH_3), 34.4 ($C(CH_3)_2$), 37.9 (CH_2), 50.2 (CH_2), 68.6 (CH), 95.3 (C-OH), 105.5, 116.1, 123.8, 125.5, 126.8, 128.6, 128.7, 128.9, 129.4, 131.5, 132.7, 134.6, 136.2, 141.6, 146.7, 165.0, 192.0 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): Minor diastereomer (45%): δ 1.00 (3H, s, CH_3), 1.13 (3H, s, CH_3), 2.25−2.72 (4H, m, $2CH_2$), 4.55 (1H, d, CH), 5.70 (1H, d, NH), 6.25−7.50 (13H, m, Ar and OH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 27.0 (CH_3), 29.8 (CH_3), 32.5 ($C(CH_3)_2$), 40.8 (CH_2), 50.9 (CH_2), 68.6(CH), 95.3(C-OH), 106.5, 117.3, 124.3, 125.7, 126.7, 128.5, 129.0, 129.2, 130.0, 130.4, 133.9, 133.1, 137.3, 144.2, 146.7, 165.0, 193.5 (C=O).

2.3.11. 3-(4-chlorophenylamino)-2,3,6,7-tetrahydro-2-hydroxy-6,6-dimethyl-1,2-diphenyl-1H-indol-4(5H)-one (6k)

White powder, mp: 178−180 °C, 0.279 g, yield: 61%. MS (EI, 70 eV): *m/z* (%) = 457 (M^+-2, 5), 332 (100), 303 (55), 275 (23), 247 (29), 227 (24), 127 (14), 105 (16), 77 (26). ^{1}H NMR (300 MHz, DMSO-d_6): Major diastereomer (70%): δ 1.03 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.06−2.21 (4H, m, $2CH_2$), 4.32 (1H, d, $^3J_{HH}$ = 5.7 Hz, CH), 5.59 (1H, d, $^3J_{HH}$ = 6.3 Hz, NH), 6.25−7.45 (14H, m, Ar), 6.48 (1H, s, OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 28.5 (CH_3), 28.9 (CH_3), 34.1 ($C(CH_3)_2$), 37.7 (CH_2), 51.1 (CH_2), 64.9 (CH), 96.8 (C-OH), 106.7, 115.2, 120.4, 125.2, 126.6, 127.9, 128.7, 128.8, 128.9, 129.0, 137.2, 143.6, 148.4, 164.9, 190.1 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): Minor diastereomer (30%): δ 1.00 (3H, s, CH_3), 1.12 (3H, s, CH_3), 2.27−2.60 (4H, m, $2CH_2$), 4.55 (1H, d, CH), 5.70 (1H, d, NH), 6.25−7.45 (15H, m, Ar and OH). ^{13}C NMR (75.4 MHz, DMSO-d_6): δ 28.1 (CH_3), 29.6 (CH_3), 34.6 ($C(CH_3)_2$), 37.9 (CH_2), 51.1 (CH_2), 64.6 (CH), 99.9 (C-OH), 107.9, 114.3, 122.0, 126.4, 127.0, 127.4, 128.2, 128.4, 128.6, 130.0, 138.0, 144.9, 149.7, 164.9, 190.8 (C=O).

2.4. Crystal structures of 6a

The colorless needle crystals of **6a** were grown from the ethanol solution. The X-ray data for the reported structure (Fig. 2) was collected at 293 (2) K with an Oxford Sapphire CCD diffractometer using Mo Kα radiation λ = 0.71073 Å and ω-2θ method. The structure was solved by direct methods and refined with the full-matrix least-

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squares method on F^2 with the use of SHELX2014 program packages [27]. The analytical absorption corrections were applied (CrysAlis version 171.38.43 package of programs [28] Rigaku OD, 2015). Positions of hydrogen atoms have been found from the electron density maps and hydrogen atoms were constrained during refinement with the appropriate riding model as implemented in SHELX during refinement. The data collection and refinement processes are summarized in Table 1. The structural data have been deposited at the Cambridge Crystallographic Data Centre: (CCDC No 1863576).

3. Results and discussion

In this paper, we have been focused on describing a facile, new, and green method for the chemoselective synthesis of a library of pharmacologically relevant indole derivatives **6** *via* the one-pot, multi-component reaction of 5,5-dimethyl-3-(arylamino)cyclohex-2-enone derivatives **3** (derived from the addition of various anilines **2** to dimedone **1**) with phenylglyoxal monohydrate **4**, and diverse anilines **5**, in water at room temperature without the use of any catalyst (Fig. 3).

Nowadays in organic synthesis, replacement of commonly used organic solvents with environmentally benign reaction media and designing one-pot reactions as one of the most direct, effective methods, have raised as issues of innovation in green chemistry for production of fine chemicals [29].

To optimize the reaction conditions, we examined this reaction in the various parameters, such as the absence and the presence of catalyst, and several solvents. The

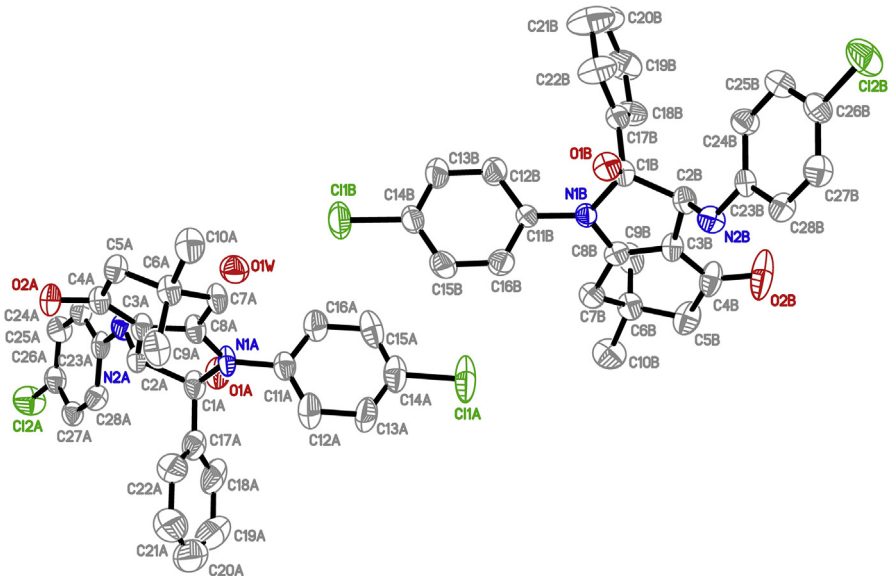

Fig. 2. Crystal structure of **6a** with the thermal ellipsoids plotted at 30% probability. The hydrogen atoms are omitted for clarity.

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Table 1. Crystal data and structure refinement parameters for **6a**.

Identification code	**6a**
CCDC	1863576
Empirical formula	$C_{28}H_{26.5}Cl_2N_2O_{2.25}$
Formula weight, g mol^{-1}	497.91
Crystal size, mm	0.496 × 0.128 × 0.119
Crystal system	Monoclinic
Space group	$P2_1/n$
a, Å	13.5103 (17)
b, Å	21.5765 (19)
c, Å	18.163 (2)
α, deg	90
β, deg	102.320 (12)
γ, deg	90
Volume, $Å^3$	5172.6 (11)
Z	8
Density (calc.), g cm^{-3}	1.279
Absorption coefficient, mm^{-1}	0.279
F (000)	2084
Θ range, deg	2.209 to 26.372
Reflections collected/unique	34576/10567 [R (int) = 0.1298]
Index ranges hkl	−16<=h<=15, −26<=k<=26, −22<=l<=22
restraints/parameters	3/623
Goodness of fit on F^2	0.971
Final R indices [I > 2σ(I)]	R1 = 0.0757, wR2 = 0.1335
R indices (all data)	R1 = 0.2341, wR2 = 0.1945
Max electron density/e·$Å^{-3}$	0.285
Min electron density/e·$Å^{-3}$	−0.360

optimized results are presented in Table 2. Experimental results showed that the reaction proceeded very cleanly with high yield and the shortest reaction time when the H_2O was used as a solvent at room temperature (Table 2, Entry 6). The yield of the product was low when EtOH or EtOH/H_2O were used as solvent at room temperature or reflux conditions (Table 2, Entry 1, 4, 5). Also the yield of the product was low, when CH_3CN was used as a solvent at room temperature and a lot of spots were observed on TLC, so another 50% product related to impurities such as starting materials and byproducts (Table 2, Entry 7). The reaction did not proceed well when the reaction was performed in the presence of Et_3N or *p*-TSA as catalyst in EtOH, so a lot of spots were observed on TLC (Table 2, Entry 2 and 3). In all entries 1−7, the yield of the product did not increase after 24 h.

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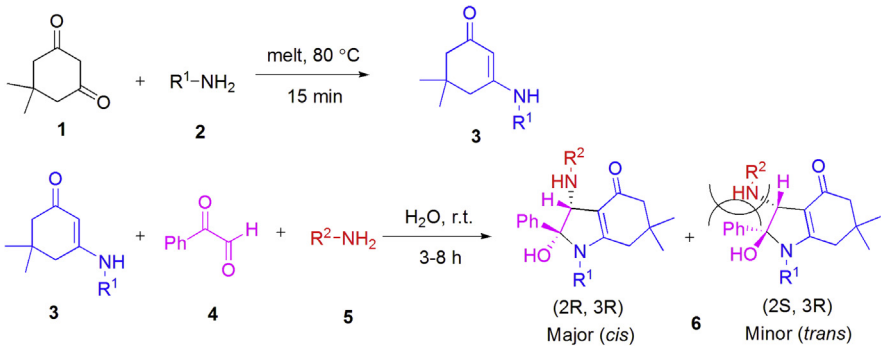

Fig. 3. Synthetic scheme for the formation of product **6**.

Table 2. Optimization of reaction conditions for the synthesis of **6a**.

Entry	Reaction conditions	Catalyst	Time (h)	Yield (%)
1	EtOH, r.t.	–	7	80
2	EtOH, r.t.	Et_3N	24	n.r.
3	EtOH, reflux	*p*-TSA	24	trace
4	H_2O/EtOH (1:1), r.t.	–	2	80
5	H_2O/EtOH (1:1), reflux	–	1	70
6	**H_2O, r.t.**	–	**4**	**95**
7	CH_3CN, r.t.	–	1	50

r.t.: room temperature, n.r.: no reaction.

As shown in Table 3, several kinds of anilines were tolerated. The reaction was completed after 3−8 hours to afford corresponding heterocyclic systems **6a-k** (Fig. 4), in good to excellent yields (61−95%). Several other various heteroaromatic, aliphatic and aromatic amines such as 2-chloroaniline, 4-methoxyaniline, 4-aminophenol, 4-nitroaniline, 2-nitroaniline, *o*-phenylenediamine, 2-aminothiophenol, *N*,*N*-dimethyl-*p*-phenylenediamine, 3-aminopyridine-2-thiol, 2-amino-3-hydroxypyridine, benzylamine, isopropylamine, and ethylamine were tested for the reaction in water, but they did not work.

The 3-arylamino-2-hydroxy-tetrahydroindol-4-one compound **6** possesses two chiral centers and therefore two diastereoisomers are expected (Fig. 3). The ^{1}H- and ^{13}C-NMR spectrum of the crude product showed the resonances of the two diastereoisomers. We were not able to separate **6** in pure form. However, its NMR data can be extracted from the mixture of the two isomers (see Supporting Information). The structures of compounds **6a-k** were assigned from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra (see the Supporting Information) and by single-crystal X-ray analysis of **6a** (Fig. 2).

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Table 3. Products **6a-k**.

Entry	R^1-NH_2[a]	R^2-NH_2[a]	Product[b]	Time (h)	Yield (%)
1	4-Cl-C_6H_4-NH_2	4-Cl-C_6H_4-NH_2	**6a**	5	95
2	4-Br-C_6H_4-NH_2	3,4-Cl_2-C_6H_3-NH_2	**6b**	4	87
3	4-Cl-C_6H_4-NH_2	3,4-Cl_2-C_6H_3-NH_2	**6c**	3	76
4	4-Cl-C_6H_4-NH_2	4-Br-C_6H_4-NH_2	**6d**	6	83
5	3,5-$(CH_3)_2$-C_6H_3-NH_2	3,4-Cl_2-C_6H_3-NH_2	**6e**	5	80
6	4-Br-C_6H_4-NH_2	4-Cl-C_6H_4-NH_2	**6f**	5	80
7	C_6H_5-NH_2	3,4-Cl_2-C_6H_3-NH_2	**6g**	5	81
8	C_6H_5-NH_2	4-Br-C_6H_4-NH_2	**6h**	4	85
9	3,4-Cl_2-C_6H_3-NH_2	4-Br-C_6H_4-NH_2	**6i**	6	68
10	3,4-Cl_2-C_6H_3-NH_2	4-Cl-C_6H_4-NH_2	**6j**	6	89
11	C_6H_5-NH_2	4-Cl-C_6H_4-NH_2	**6k**	8	61

[a] 5,5-dimethyl-3-(arylamino)cyclohex-2-enone (1 mmol), phenylglyoxal monohydrate (1 mmol), various anilines (1 mmol), were used in water at room temperature.
[b] Fig. 4.

3.1. Structures of 6a

Structure determination for **6a** confirmed that the synthesized product is an indole derivative (Fig. 2). The asymmetric part of the structure consists of two enantiomers of **6a,** (2R, 3R) and (2S, 3S), as well as one water molecule. There is a non-crystallographic center of symmetry relating two **6a** molecules, and this symmetry is broken by the presence of only one water molecule in the asymmetric unit. Since the space group is centrosymmetric, crystal as a whole is a racemic mixture of these isomers. The valence geometry of **6a** is typical. For both enantiomers, the phenyl ring C17–C22 and 5-membered pyrrole ring are situated almost perpendicularly. The dihedral angles measured between best planes of these two rings are 89.7 (4) and 88.9 (3)° for (2R, 3R)-enantiomer and (2S, 3S)-enantiomer, respectively. In such conformation, the dihedral angle between the best planes of 5-membered pyrrole ring of indole moiety and phenyl ring C11A–C16A is 80.2 (3)°, larger than that establish for (2S, 3S)-enantiomer (59.6 (2)°). Whereas, the mutual arrangement of the phenyl ring C23–C28 and the pyrrole ring for both enantiomers is the same. The dihedral angles between best planes of these two rings are 59.9 (3) and 58.5 (2)° for (2R, 3R)-enantiomer and (2S, 3S)-enantiomer, respectively.

The analysis of the **6a** structure revealed intermolecular O-H…O and N-H…O interactions (Table 4). Analysis of the crystal packing revealed the presence of intermolecular C14B-Cl1B…π interaction involving 6-membered ring of (2S, 3S)-enantiomer, with Cl1B… $\pi_{C17A–C22A}$ [-½-x, ½+y, ½-z] distance of 3.900 (4) Å. Also, a series of intra- and intermolecular C-H… π interactions are detected. The C5A… $\pi_{C23B—C28B}$ [-½-x, ½+y, ½-z] and C12B… $\pi_{C17B—C22B}$ interactions are found, with distances 3.858 (6) and 3.784 (7) Å, respectively.

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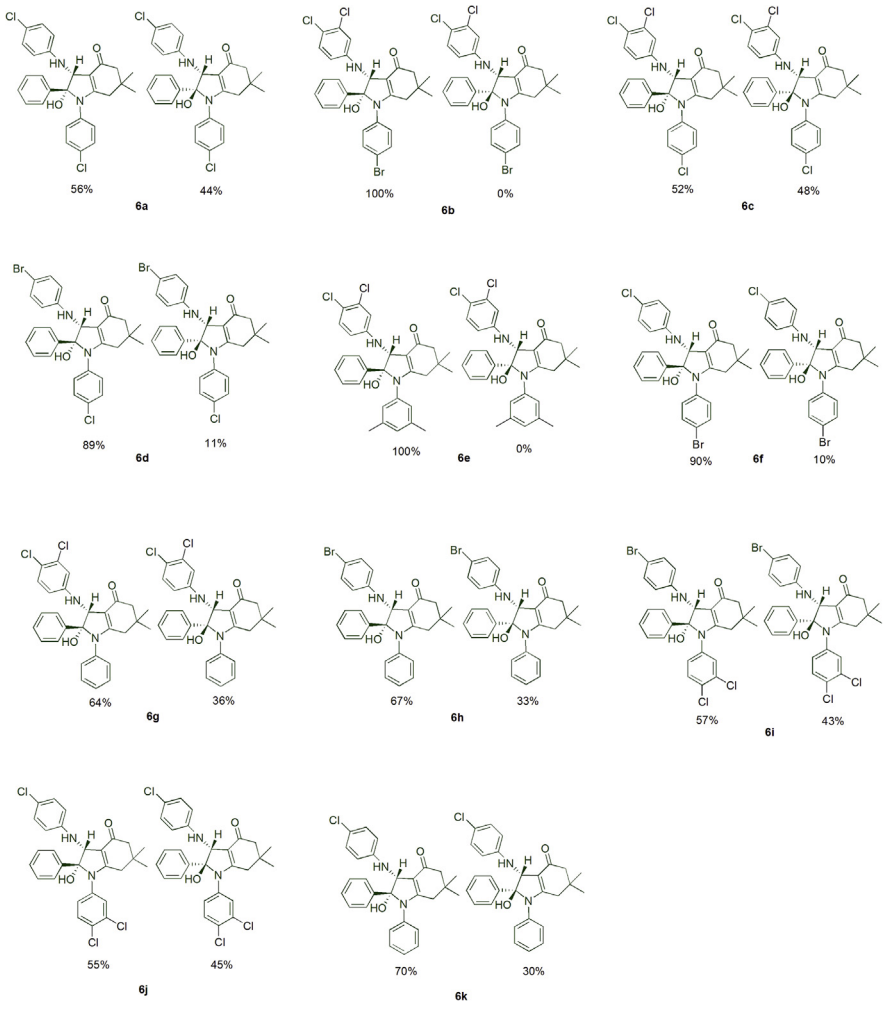

Fig. 4. Products **6a-k**.

The IR spectrum of this structure indicated absorption bands due to NH and OH stretching (3372, 3315 cm^{-1}) as well as bands at 2949, 1602, 1557 and 1280 cm^{-1} due to the CH, C=O, Ar and C-N groups. The ^{1}H NMR spectrum of compounds **6a-k** indicated the presence of two diastereomers (2R, 3R) and (2S, 3R).

Table 4. Hydrogen bonds [Å and °] for **6a**.

D−H···A	d (D−H)	d (H···A)	d (D···A)	<(DHA)
O1A-H1AA…O1W	0.820	1.971	2.707	149.08
N2A-H2AB…O2B^{i}	0.860	2.164	3.018	171.83
O1B-H1BA…O2A^{ii}	0.820	2.156	2.877	146.69
N2B-H2BB…O2A^{iii}	0.860	2.200	3.015	158.08
O1W-H2W…O2B^{iv}	0.870	1.496	2.321	156.85
O1W-H1W…O2B^{i}	0.870	2.014	2.809	151.68

Symmetry code: ^{i} = *x+1/2,-y+3/2, z+1/2;* ^{ii} = *-x-1/2, y-1/2, -z+1/2,* ^{iii} = *x+1/2, -y+3/2, z-1/2,* ^{iv} = *-x+1/2, y+1/2, -z+1/2.*

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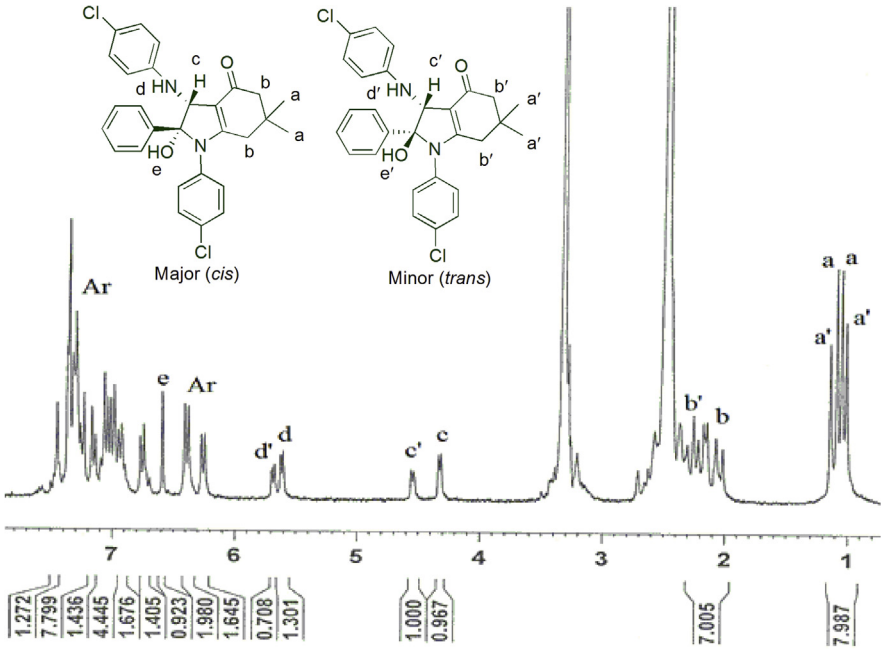

Fig. 5. ^{1}H NMR spectrum of **6a**.

For examples the ^{1}H NMR spectrum of **6a** showed two singlets for two CH_3 groups (δ 1.04 and 1.08 ppm), multiplet for two CH_2 groups (δ 2.01−2.25 ppm), one doublet for CH group (δ 4.32 ppm), one doublet for NH group (δ 5.62 ppm), aromatic region of the spectrum (δ 6.15−7.45 ppm) for the aromatic moieties, one

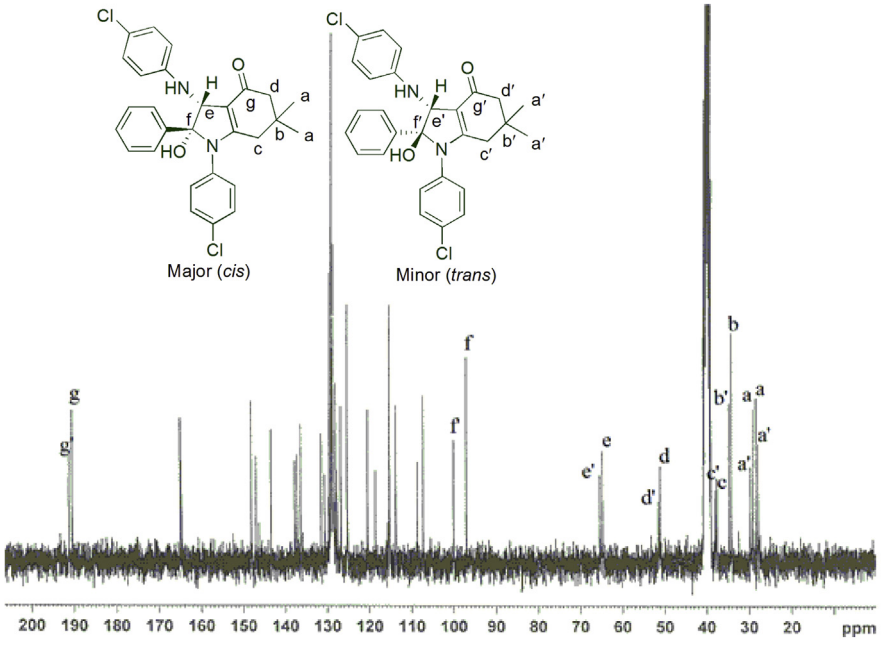

Fig. 6. ^{13}C NMR spectrum of **6a**.

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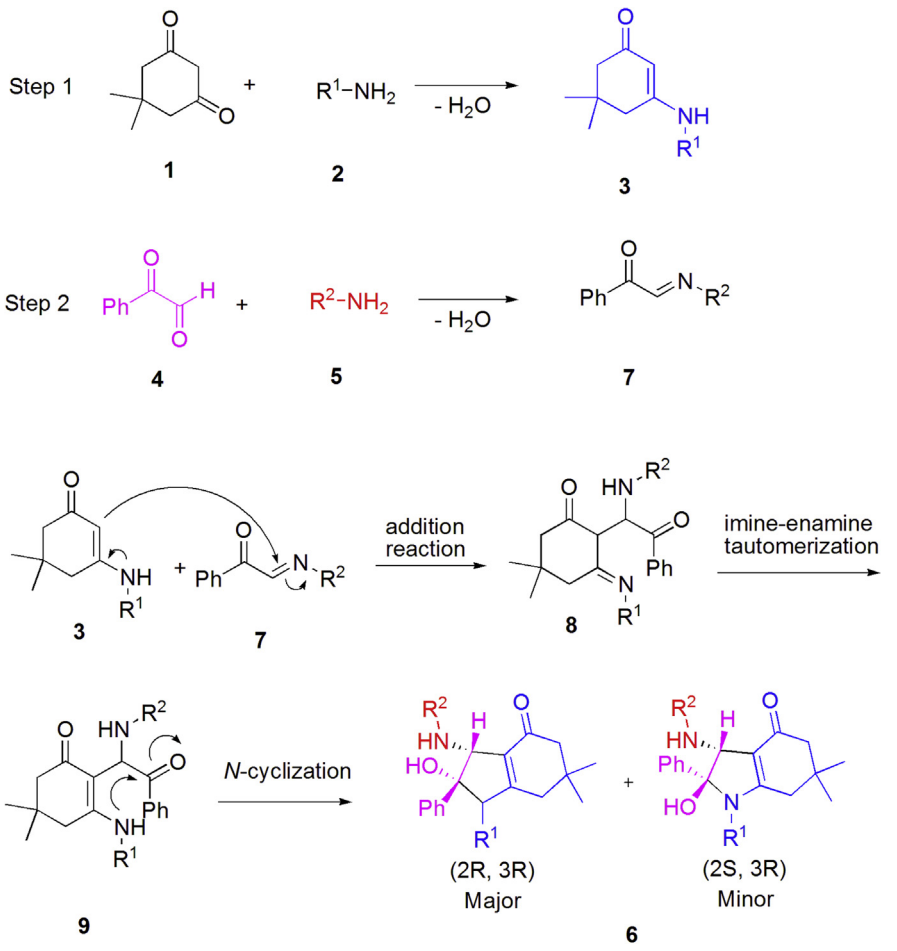

Fig. 7. Proposed mechanism for the formation of product **6**.

singlet for the OH group (δ 6.51 ppm), for major diastereomer (56%); and also two singlets for two CH_3 groups (δ 1.01 and 1.13 ppm), multiplet for two CH_2 groups (δ 2.30−2.62 ppm), one doublet for CH group (δ 4.54 ppm), one doublet for NH group (δ 5.69 ppm), aromatic region of the spectrum (δ 6.15−7.45 ppm), for the aromatic moieties and one singlet for the OH group (δ 6.51 ppm) for minor diastereomer (44%) (Fig. 5). The ^{1}H-decoupled ^{13}C NMR spectrum of **6a** showed 44 distinct signals in agreement with the proposed structures for two diastereomers (Fig. 6).

The 2,3-*cis*-diastereoselectivity that was observed in the major isomer could be rationalized by two reasons. Firstly, thermodynamic control could be operative, forming the more stable (OH-NH *cis*) diastereoisomer. Secondly, the *trans* configuration could not be reached by considering the steric repulsion between the NHAr and phenyl group.

An acceptable reaction mechanism for the formation of product **6** is depicted in Fig. 7. It is reasonable to assume that the reaction involves initial formation of 5,5-dimethyl-3-(arylamino)cyclohex-2-enone intermediate **3** between the dimedone **1** and aniline **2**. Apparently, the reaction of phenylglyoxal monohydrate **4**, and

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aniline **5** furnishes adduct **7**. Then chemoselective addition reaction between intermediate **3** and adduct **7** affords **8** which undergoes successive imine-enamine tautomerization followed *N*-cyclization by nucleophilic addition of the secondary amino group to carbonyl group led to the formation of product **6**.

4. Conclusion

This work represents a successful MCR chemoselective synthesis of new indole derivatives *via* the one-pot, multi-component reaction of dimedone, phenylglyoxal monohydrate, and various anilines, in water at room temperature. These structures having indole moieties, which is one of the most typical privileged scaffolds, are completely new and there is no other report for their synthesis. The significant advantages of this procedure are mild reaction conditions, experimental simplicity, easy workup procedure and high yields. In addition to efficiency, the use of water as solvent, the limited energy consumption, and catalyst-free approach, make the process an attractive green synthesis of the target compounds.

Declarations

Author contribution statement

Mohammad Bayat: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Fahimeh Sadat Hosseini, Anna Kozakiewicz: Analyzed and interpreted the data; Wrote the paper.

Fatemeh Rahimi: Performed the experiments.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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