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A Spontaneous, Convenient Synthesis and Biological Evaluation of Indole Derivatives

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A spontaneous, convenient synthesis and biological evaluation of Indole derivatives

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Abstract

Oxoindoline derivatives are interesting heterocyclic compounds which show diverse biological and pharmacological properties. In this research oxoindoline derivative was prepared by one-pot condensation reaction of isatin, dimedone, and various active methylene using piperidine as a basic catalyst and methanol as a solvent under stirring at room temperature. The products were characterized by FT-IR, Mass, ^{1}H NMR and ^{13}C NMR spectroscopy.

Keywords: Multi-component reactions, Isatin, Dimedone, oxoindolines, Antimicrobial evaluation.

Introduction

In 1900, Bayer created the first spiran described as a bicyclic hydrocarbon connected by a single carbon. The term spirocyclanes was used to describe the family of such hydrocarbon. Due to the tetrahedral nature of the Spiro-linked carbon, the ring planes are nearly perpendicular to each other.

The chemistry of spiro indoles in which an indole ring is joined to S and N containing heterocycles at the C-3 position through a spiro carbon atom is of great

interest due to their physiological and biological activities.[1,2] Spiro compounds having cyclic structures fused at a central carbon are of recent interest due to their interesting conformational features and their structural implications on biological systems. The asymmetric characteristic of the molecules due to the chiral Spiro-C is one of the important criteria of the biological activities.

Spiro compounds present unique preparative challenges; whether each ring contributing to its structure is unique or identical, spiro-ring fusion provides a useful method of increasing molecular complexity and may offer greater benefit than the introduction of flat rings. Recent progress on new synthetic routes to spiro building blocks will facilitate combination of spiro scaffolds into more pharmaceutically active molecules. Spiro-containing systems not only have greater three-dimensionality than flat aromatic compounds, but also introduce structural novelty.

The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[3,4] Spirooxindoles, especially those spiro-annulated with heterocycles at the 3- position, have shown good biological activities.[5] These potential properties have prompted many efforts toward the synthesis of spirooxindole-fused heterocycles and numerous impressive successes have been obtained for the synthesis of the diversely structured spirocyclic oxindoles.[6,7] Isatin is probably one of the most widely used reagent for constructing spirooxindoles in many reactions such as 1,3-dipolar cycloaddition, Morita-Baylis-Hillman reaction and other condensation reactions.[8-10] In the past few years the multicomponent reactions based on the versatile reactivity of isatins have become the new efficient methods for the synthesis of various spirooxindoles.[11,12]

Experimental

Material and Methods:

The chemicals for research were purchased from Merck and utilize in the synthesis. The reaction monitoring were carried out using thin-layer chromatography (TLC) on precoated silica gel GF254 plates purchased E-Merck Co and visualized by under exposure of UV light. The m.p. was examined by open capillary method and are uncorrected. IR spectrums of synthesised compounds were examined using KBr pellet method on SHIMADZU-FTIR-8400 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker-Avance-II (400-MHz) NMR spectrometer in DMSO-d_6 as a solvent. Tetramethylsilane used as a reference slandered for chemical shift values. Mass spectra were determined using direct inlet probe on a Shimadzu GCMS-QP 2010 mass spectrometer and C, H, N analysis was carried out using elemental analyser Heraus.

General procedure for the synthesis of 2-(3-(4,4-dimethyl-2,6-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl) derivatives (SP 201-221)

A mixture of the isatin or substituted isatin (0.01 mol), substituted active methylene (0.01 mol) and dimedone (0.01 mol) were stirred for 2-3 hr. in 20 ml of MeOH with catalytic amount of piperidine. After completion of the reaction, the reaction mixture was filtered to give the solid crystalline products (SP 201-221), which were recrystallized from ethanol. The characterizations of synthesised compounds were carried out using Mass spectral data, IR, ^{1}H NMR, and elemental analyses.The physical parameters such as melting points, % yield and R_f values of the synthesized compounds are depicted in Table 1.

Detection Method:

2-(3-(4,4-dimethyl-2,6-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl) malononitrile (SP-201)

Yield: 82%; mp 273-275 ºC; IR (cm^{-1}): 3140 (=C-H stretching of aromatic ring), 2962, 2877 (C-H stretching of alkane), 2191 (CN stretching of cyanide), 1720 (C=O stretching of carbonyl of ketone), 1658 (C=O stretching of carbonyl of amide), 1604 (C=C stretching of aromatic ring), 1465, (C-H bending of alkane), 1219 (C-C stretching of alkane), 748 (C-C bending of *o*-di-substituted aromatic ring), 678 (C-H bending of *o*-di-substituted aromatic ring); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.99 (s, 6H, H_a), 2.07-2.19 (s, 2H, H_b), 2.49-2.60 (m, 2H, H_c), 6.77-6.79 (d, 1H, H_d), 6.86-6.90 (t, 1H, H_e), 6.96-6.98 (d, 1H, H_f), 7.11-7.15 (m, 2H, H_g), 7.22 (s, 2H, H_h), 10.39 (s, 1H, H_i); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 26.99, 27.57, 31.73, 31.91, 38.86, 39.07, 39.28, 39.48, 39.69, 36.90, 40.11, 46.78, 48.58, 49.96, 57.46, 109.20, 110.76, 117.30, 121.64, 122.98, 128.13, 134.38, 142.03, 158.73, 164.10, 177.99, 194.84; MS: *m/z* 335; Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53%; Found: C, 68.17; H, 5.20; N, 12.61%.

ethyl 2-cyano-2-(3-(4,4-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl)acetate (SP-202)

Yield: 78%; mp 268-270 ºC; IR (cm^{-1}): 3109, 3178 (=C-H stretching of aromatic ring), 2955, 2870 (C-H stretching of alkane), 2337 (CN stretching of cyanide), 1720 (C=O stretching of carbonyl of ketone), 1689 (C=O stretching of carbonyl of amide), 1612,1527 (C=C stretching of aromatic ring), 1473, (C-H bending of alkane), 1226 (C-C stretching of alkane), 1296, 1311 (C-O stretching of ester), 1049, 1026 (C-O-C stretching of ester), 748 (C-C bending of *o*-di-substituted aromatic ring), 678 (C-H bending of *o*-di-substituted aromatic ring); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm:

0.77-0.81 (t, 3H, H_a), 0.94 & 1.01 (s, 6H, H_b), 1.99-2.17 (m, 2H, $H_{c,d}$), 2.46-2.60 (m, 1H, H_e), 3.68-3.71 (q, 2H, H_f), 6.66-6.68 (d, 1H, H_g), 6.73-6.77 (t, 1H, H_h), 6.82-6.84 (d, 1H, H_i), 7.02-7.05 (t, 1H, H_j), 7.87 (s, 1H, H_k), 10.15 (s, 1H, H_l); ^{13}C NMR (DMSO-*d_6*, 400 MHz) δ ppm:13.07, 26.64, 27.76, 31.52, 38.83, 39.04, 39.25, 39.49, 39.67, 39.88, 40.09, 46.57, 50.60, 58.81, 76.27, 108.09, 113.05, 120.51, 122.20, 127.14, 135.95, 144.00, 159.08, 162.38, 167.62, 179.78, 194.63; MS: *m/z* 382; Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33%; Found: C, 66.07; H, 5.93; N, 7.42%.

2-(5-bromo-3-(4,4-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl) malononitrile (SP-205)

Yield: 89%; mp 281-283 ºC; IR (cm^{-1}): 3155 (=C-H stretching of aromatic ring), 2955, 2870 (C-H stretching of alkane), 2191 (CN stretching of cyanide), 1728 (C=O stretching of carbonyl of ketone), 1658 (C=O stretching of carbonyl of amide), 1604 (C=C stretching of aromatic ring), 1473, (C-H bending of alkane), 1350 (C-N stretching of amine), 1219 (C-C stretching of alkane), 810 (C-H bending of p-di-substituted aromatic ring), 686, 632 (C-H bending of o-di-substituted aromatic ring), 547 (C-Br stretching of halogen); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 1.02 (s, 6H, H_a), 2.15 (s, 2H, H_b), 2.57 (s, 2H, H_c), 6.76 (s, 1H, H_d), 7.21 (d, 2H, H_e, H_f), 7.33 (s, 2H, H_g), 10.56 (s, 1H, H_h); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 27.15, 27.50, 31.96, 38.85, 39.06, 39.27, 39.48, 39.69, 39.89, 40.10, 47.01, 49.90, 56.68, 110.15, 111.16, 113.29, 117.20, 125.93, 130.90, 136.77, 141.42, 158.84, 164.60, 177.65, 195.09; MS: m/z 413; Anal. Calcd for $C_{19}H_{16}BrN_3O_3$: C, 55.09; H, 3.89; N, 10.14%; Found: C, 55.18; H, 3.99; N, 10.25%.

ethyl2-(5-bromo-3-(4,4-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl)-2-cyanoacetate (SP-206)

Yield: 76%; mp 271-273 ºC; IR (cm^{-1}): 3155 (=C-H stretching of aromatic ring), 2955, 2877 (C-H stretching of alkane), 2119 (CN stretching of cyanide), 1728 (C=O stretching of carbonyl of ketone), 1681 (C=O stretching of carbonyl of amide), 1604 (C=C stretching of aromatic ring), 1473, (C-H bending of alkane), 1219 (C-C stretching of alkane), 1296 (C-O stretching of ester), 1057, 1026(C-O-C stretching of ester), 810 (C-H bending of *p*-di-substituted aromatic ring), 686, 624 (C-H bending of *o*-di-substituted aromatic ring), 563 (C-Br stretching of halogen); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.827 (s, 6H, H_a), 0.97&1.00 (s, 4H, H_b), 2.11-2.51 (m, 3H, H_c), 3.36-3.73 (m, 2H, H_d), 6.65 (s, 1H, H_e), 7.01(d, 1H, H_f), 7.22(d, 1H, H_g), 7.95 (s, 2H, H_h), 10.33 (s, 1H, H_i); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 13.10, 27.07, 27.39, 31.55, 38.85, 39.06, 39.26, 39.47, 39.68, 39.89, 40.08, 46.82, 50.52, 58.96, 75.62, 109.98, 112.03, 112.45, 125.03, 129.83, 138.49, 143.52, 159.17, 162.90, 167.41, 179.38, 194.86; MS: *m/z* 460; Anal. Calcd for $C_{21}H_{21}BrN_2O_5$: C, 54.68; H, 4.59; N, 6.07%; Found: C, 54.79; H, 4.70; N, 6.19%.

2-(5-chloro-3-(4,4-dimethyl-2,6-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl) malononitrile (SP-207)

Yield: 84%; mp 275-277 ºC; IR (cm^{-1}): 3155 (=C-H stretching of aromatic ring), 2955, 2877 (C-H stretching of alkane), 2119 (CN stretching of cyanide), 1728 (C=O stretching of carbonyl of ketone), 1681 (C=O stretching of carbonyl of amide), 1604 (C=C stretching of aromatic ring), 1473, (C-H bending of alkane), 1219 (C-C stretching of alkane), 1296 (C-O stretching of ester), 1057, 1026(C-O-C stretching of ester), 810 (C-H bending of *p*-di-substituted aromatic ring), 683 (C-H bending of *o*-di-substituted aromatic ring), 645 (C-Cl stretching of halogen); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.99 (s, 6H, H_a), 2.37 (s, 2H, H_b), 2.49-2.60 (m, 2H, H_c), 7.22-7.24 (d, 1H, H_d), 7.47 (s, 1H, H_e), 7.66-7.68 (d, 1H, H_f), 7.21 (s, 2H, H_g), 10.40 (s, 1H, H_h); ^{13}C NMR

(DMSO-d_6, 400 MHz) δ ppm: 21.3, 26.6, 30.4, 44.3, 54.1, 68.2, 111.3, 112.7, 127.9, 129.6, 130.4, 137.6, 140.5, 182.1, 208.3; MS: *m/z* 369; Anal. Calcd for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36%; Found: C, 61.63; H, 4.24; N, 11.46%.

ethyl2-(5-chloro-3-(4,4-dimethyl-2,6-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl)-2-cyanoacetate (SP-208)

Yield: 75%; mp 272-274 ºC; IR (cm^{-1}): 3155 (=C-H stretching of aromatic ring), 2955, 2877 (C-H stretching of alkane), 2119 (CN stretching of cyanide), 1728 (C=O stretching of carbonyl of ketone), 1681 (C=O stretching of carbonyl of amide), 1604 (C=C stretching of aromatic ring), 1473, (C-H bending of alkane), 1219 (C-C stretching of alkane), 1296 (C-O stretching of ester), 1057, 1026(C-O-C stretching of ester), 810 (C-H bending of *p*-di-substituted aromatic ring), 686, 624 (C-H bending of *o*-di-substituted aromatic ring), 645 (C-Cl stretching of halogen); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.827 (s, 6H, H_a), 0.97&1.00 (s, 4H, H_b), 2.11-2.51 (m, 3H, H_c), 3.36-3.73 (m, 2H, H_d), 6.65 (s, 1H, H_e), 7.01(d, 1H, H_f), 7.22(d, 1H, H_g), 7.95 (s, 2H, H_h), 10.33 (s, 1H, H_i); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 14.1, 26.6, 30.4, 40.8, 44.2, 54.1, 60.8, 68.7, 111.3, 114.1, 127.9, 129.6, 130.4, 137.6, 140.5, 164.5, 182.1, 208.3; MS: *m/z* 416; Anal. Calcd for $C_{21}H_{21}ClN_2O_5$: C, 60.51; H, 5.08; N, 6.72%; Found: C, 60.43; H, 5.19; N, 6.83%.

2-(7-bromo-3-(4,4-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl)malononitrile (SP-209)

Yield: 68%; mp 278-280 ºC; IR (cm^{-1}): 3155 (=C-H stretching of aromatic ring), 2955, 2870 (C-H stretching of alkane), 2191 (CN stretching of cyanide), 1728 (C=O stretching of carbonyl of ketone), 1658 (C=O stretching of carbonyl of amide), 1604 (C=C stretching of aromatic ring), 1473, (C-H bending of alkane), 1350 (C-N stretching of amine), 1219 (C-C stretching of alkane), 810 (C-H bending of p-di-substituted

aromatic ring), 686, 632 (C-H bending of o-di-substituted aromatic ring), 547 (C-Br stretching of halogen); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 1.02 (s, 6H, H_a), 2.15 (s, 2H, H_b), 2.57 (s, 2H, H_c), 6.76 (s, 1H, H_d), 7.21 (d, 2H, H_e, H_f), 7.33 (s, 2H, H_g), 10.56 (s, 1H, H_h); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 27.15, 27.50, 31.96, 38.85, 39.06, 39.27, 39.48, 39.69, 39.89, 40.10, 47.01, 49.90, 56.68, 110.15, 111.16, 113.29, 117.20, 125.93, 130.90, 136.77, 141.42, 158.84, 164.60, 177.65, 195.09; MS: m/z 413; Anal. Calcd for $C_{19}H_{16}BrN_3O_3$: C, 55.09; H, 3.89; N, 10.14%; Found: C, 55.18; H, 3.99; N, 10.25%.

ethyl2-(7-bromo-3-(4,4-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl)-2-cyanoacetate (SP-210)

Yield: 67%; mp 269-271 ºC; IR (cm^{-1}): 3155 (=C-H stretching of aromatic ring), 2955, 2877 (C-H stretching of alkane), 2119 (CN stretching of cyanide), 1728 (C=O stretching of carbonyl of ketone), 1681 (C=O stretching of carbonyl of amide), 1604 (C=C stretching of aromatic ring), 1473, (C-H bending of alkane), 1219 (C-C stretching of alkane), 1296 (C-O stretching of ester), 1057, 1026(C-O-C stretching of ester), 810 (C-H bending of *p*-di-substituted aromatic ring), 686, 624 (C-H bending of *o*-di-substituted aromatic ring), 563 (C-Br stretching of halogen); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.827 (s, 6H, H_a), 0.97&1.00 (s, 4H, H_b), 2.11-2.51 (m, 3H, H_c), 3.36-3.73 (m, 2H, H_d), 6.65 (s, 1H, H_e), 7.01(d, 1H, H_f), 7.22(d, 1H, H_g), 7.95 (s, 2H, H_h), 10.33 (s, 1H, H_i); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 13.10, 27.07, 27.39, 31.55, 38.85, 39.06, 39.26, 39.47, 39.68, 39.89, 40.08, 46.82, 50.52, 58.96, 75.62, 109.98, 112.03, 112.45, 125.03, 129.83, 138.49, 143.52, 159.17, 162.90, 167.41, 179.38, 194.86; MS: *m/z* 460; Anal. Calcd for $C_{21}H_{21}BrN_2O_5$: C, 54.68; H, 4.59; N, 6.07%; Found: C, 54.79; H, 4.70; N, 6.19%.

2-(7-chloro-3-(4,4-dimethyl-2,6-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl) malononitrile (SP-213)

Yield: 68%; mp 286-288 ºC; IR (cm^{-1}): 3155 (=C-H stretching of aromatic ring), 2955, 2877 (C-H stretching of alkane), 2119 (CN stretching of cyanide), 1728 (C=O stretching of carbonyl of ketone), 1681 (C=O stretching of carbonyl of amide), 1604 (C=C stretching of aromatic ring), 1473, (C-H bending of alkane), 1219 (C-C stretching of alkane), 1296 (C-O stretching of ester), 1057, 1026(C-O-C stretching of ester), 810 (C-H bending of *p*-di-substituted aromatic ring), 683 (C-H bending of *o*-di-substituted aromatic ring), 645 (C-Cl stretching of halogen); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.99 (s, 6H, H_a), 2.37 (s, 2H, H_b), 2.49-2.60 (m, 2H, H_c), 7.22-7.24 (d, 1H, H_d), 7.47 (s, 1H, H_e), 7.66-7.68 (d, 1H, H_f), 7.21 (s, 2H, H_g), 10.40 (s, 1H, H_h); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 21.3, 26.6, 30.4, 44.3, 54.1, 68.2, 111.3, 112.7, 127.9, 129.6, 130.4, 137.6, 140.5, 182.1, 208.3; MS: *m/z* 369; Anal. Calcd for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36%; Found: C, 61.63; H, 4.24; N, 11.46%.

ethyl2-(7-chloro-3-(4,4-dimethyl-2,6-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl)-2-cyanoacetate (SP-214)

Yield: 66%; mp 283-285 ºC; IR (cm^{-1}): 3155 (=C-H stretching of aromatic ring), 2955, 2877 (C-H stretching of alkane), 2119 (CN stretching of cyanide), 1728 (C=O stretching of carbonyl of ketone), 1681 (C=O stretching of carbonyl of amide), 1604 (C=C stretching of aromatic ring), 1473, (C-H bending of alkane), 1219 (C-C stretching of alkane), 1296 (C-O stretching of ester), 1057, 1026(C-O-C stretching of ester), 810 (C-H bending of *p*-di-substituted aromatic ring), 686, 624 (C-H bending of *o*-di-substituted aromatic ring), 645 (C-Cl stretching of halogen); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.827 (s, 6H, H_a), 0.97&1.00 (s, 4H, H_b), 2.11-2.51 (m, 3H, H_c), 3.36-3.73 (m, 2H, H_d), 6.65 (s, 1H, H_e), 7.01(d, 1H, H_f), 7.22(d, 1H, H_g), 7.95 (s, 2H,

H_h), 10.33 (s, 1H, H_i); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 14.1, 26.6, 30.4, 40.8, 44.2, 54.1, 60.8, 68.7, 111.3, 114.1, 127.9, 129.6, 130.4, 137.6, 140.5, 164.5, 182.1, 208.3; MS: *m/z* 416; Anal. Calcd for $C_{21}H_{21}ClN_2O_5$: C, 60.51; H, 5.08; N, 6.72%; Found: C, 60.43; H, 5.19; N, 6.83%.

Table 1: Physical Parameters of (SP 201-221)

Code	**R**	**R_1**	**R_2**	**M.F.**	**M.W.**	**M.P. (ºC)**	**Yield (%)**	**R_f**
SP-201	H	CN	CN	$C_{19}H_{17}N_3O_3$	335	273-275	82	0.56
SP-202	H	CN	COOEt	$C_{21}H_{22}N_2O_5$	382	268-270	78	0.52
SP-203	H	Cl	$COOC_4H_9$	$C_{22}H_{26}ClNO_5$	419	258-260	69	0.50
SP-204	5-Br	Cl	$COOC_4H_9$	$C_{22}H_{25}BrClNO_5$	497	262-264	72	0.58
SP-205	5-Br	CN	CN	$C_{19}H_{16}BrN_3O_3$	413	281-283	89	0.56
SP-206	5-Br	CN	COOEt	$C_{21}H_{21}BrN_2O_5$	460	271-273	76	0.54
SP-207	5-Cl	CN	CN	$C_{19}H_{16}ClN_3O_3$	369	275-277	84	0.53
SP-208	5-Cl	CN	COOEt	$C_{21}H_{21}ClN_2O_5$	416	272-274	75	0.52
SP-209	7-Br	CN	CN	$C_{19}H_{16}BrN_3O_3$	413	278-280	68	0.50
SP-210	7-Br	CN	COOEt	$C_{21}H_{21}BrN_2O_5$	460	269-271	67	0.54
SP-211	7-Br	Cl	$COOC_4H_9$	$C_{22}H_{25}BrClNO_5$	497	259-261	70	0.58

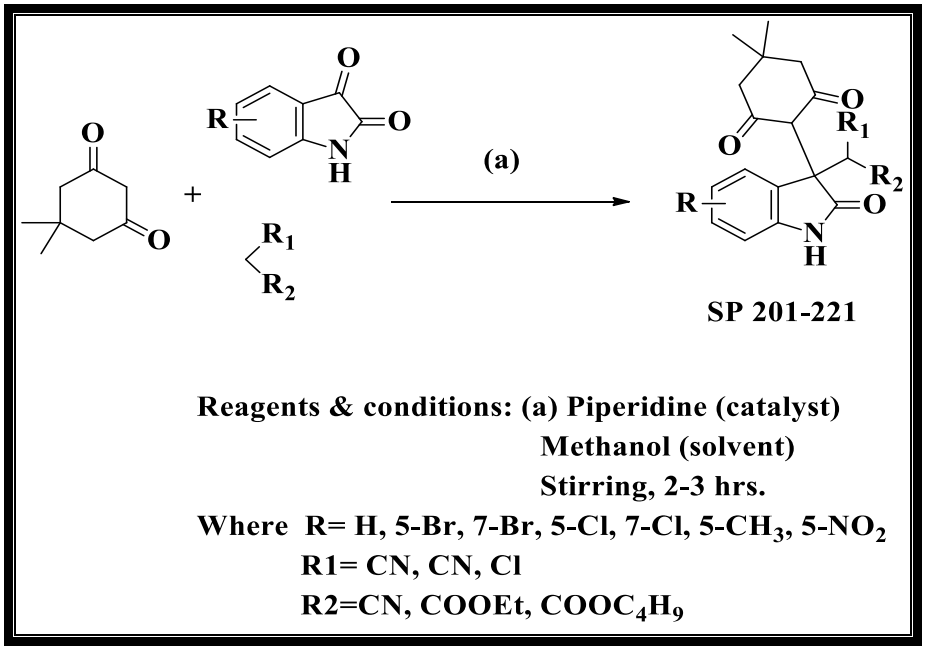
SP-212	5-Cl	Cl	$COOC_4H_9$	$C_{22}H_{25}Cl_2NO_5$	453	270-272	73	0.52
SP-213	7-Cl	CN	CN	$C_{19}H_{16}ClN_3O_3$	369	286-288	68	0.63
SP-214	7-Cl	CN	COOEt	$C_{21}H_{21}ClN_2O_5$	416	283-285	66	0.61
SP-215	7-Cl	Cl	$COOC_4H_9$	$C_{22}H_{25}Cl_2NO_5$	453	279-281	63	0.59
SP-216	5-CH_3	CN	CN	$C_{20}H_{19}N_3O_3$	349	221-223	59	0.48
SP-217	5-CH_3	CN	COOEt	$C_{22}H_{24}N_2O_5$	396	212-214	56	0.42
SP-218	5-CH_3	Cl	$COOC_4H_9$	$C_{23}H_{28}ClNO_5$	433	220-222	54	0.49
SP-219	5-NO_2	CN	CN	$C_{19}H_{16}N_4O_5$	380	297-299	65	0.60
SP-220	5-NO_2	CN	COOEt	$C_{21}H_{21}N_3O_7$	427	293-295	61	0.57
SP-221	5-NO_2	Cl	$COOC_4H_9$	$C_{22}H_{25}ClN_2O_7$	464	289-291	60	0.51

TLC Solvent system - Hexane: Ethyl acetate - 6:4

Results and Discussion

Recognizing these facts, here in we report one-pot synthesis of novel oxoindoline derivatives (SP 201-221) by three-component reaction of isatin or substituted isatin, substituted active methylene and dimedone in the presence of piperidine as a base catalyst. The mixture was stirred under 2-3 hour in methanol as solvent to give 2-(3-(4,4-dimethyl-2,6-dimethyl-2,6-dioxocyclohexyl)-2-oxoindolin-3-yl) derivatives. The products were characterized by FT-IR, Mass, ^{1}H NMR and ^{13}C NMR spectroscopy.

The newly synthesized compounds were subjected to various biological activities *viz.*, antibacterial and antifungal.



Biological evaluation

Antimicrobial evaluation

All the synthesized compounds oxoindoline derivatives (SP 201-221) were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method[13-15] with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC-443, two Gram-negative bacteria *Escherichia coli* MTCC-442, *Pseudomonas aeruginosa* MTCC-441 and three fungal strains *Candida albicans* MTCC-227, *Aspergillus Niger* MTCC-282, *Aspergillus clavatus* MTCC-1323 taking ciprofloxacin, norfloxacin and nystatin as standard drugs. The standard strains

were procured from the Microbial Type Culture Collection (MTCC) and Microcare Laboratory & Tuberculosis Research centre - Surat (India).

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro-dilution broth method according to NCCLS standards. Serial dilutions of the test compounds and reference drugs were prepared in Muellere-Hinton agar. Drugs (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 mL). Further progressive dilutions with melted Muellere-Hinton agar were performed to obtain the required concentrations. In primary screening 1000 μg mL^{-1}, 500 μg mL^{-1} and 250 μg mL^{-1} concentrations of the synthesized drugs were taken. The compounds found active in this primary screening were further tested in a second set of dilution at 125 μg mL^{-1}, 100 μg mL^{-1}, 62.5 μg mL^{-1}, 50 μg mL^{-1}, 25 μg mL^{-1}, 12.5 μg mL^{-1}, and 6.25 μg mL^{-1} concentration against all microorganisms. The tubes were inoculated with 10^8 cfu mL^{-1} (colony forming unit/mL) and incubated at 37 ºC for 24 hrs. The minimal inhibitory concentration (MIC) was the lowest concentration of the tested compound that yields no visible growth (turbidity) on the plate. To ensure that the solvent had no effect on the

bacterial growth, a control was performed with the test medium supplemented with dimethylsulfoxide (DMSO) at the same dilutions as used in the experiments and it was observed that dimethylsulfoxide (DMSO) had no effect on the microorganisms in the concentrations studied. the results obtained from antimicrobial susceptibility testing are depicted in Table 2.

Table 2: Antibacterial and Antifungal activities of synthesized compounds (SP 201-221)

Code	Minimal inhibition concentration (µg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S.a.	***S. p.***	***E.c.***	***P.a.***	***C. a.***	***A. n.***	***A.c.***
SP-201	250	250	250	500	500	500	250
SP-202	500	500	250	250	500	250	250
SP-203	**100**	**100**	125	**100**	250	250	125
SP-204	**100**	**62.5**	**100**	**100**	250	250	**100**
SP-205	250	250	250	500	500	500	250
SP-206	500	500	250	250	500	500	500
SP-207	250	250	500	500	1000	500	500
SP-208	250	500	250	500	1000	500	500
SP-209	500	500	250	500	500	>1000	500
SP-210	500	500	250	500	500	1000	1000
SP-211	250	125	125	**100**	250	250	125

SP-212	**100**	**100**	125	250	250	500	500
SP-213	500	500	250	500	500	250	1000
SP-214	500	500	250	500	250	250	>1000
SP-215	**100**	**100**	125	125	**100**	**100**	100
SP-216	500	500	500	500	500	500	1000
SP-217	250	250	500	500	500	1000	1000
SP-218	500	250	250	500	500	>1000	500
SP-219	250	250	**100**	**100**	250	125	125
SP-220	125	**100**	**100**	**100**	250	250	125
SP-221	250	**100**	**100**	125	500	250	250
Ciprofloxacin	25	25	12.5	12.5	-	-	-
Norfloxacin	12.5	12.5	12.5	12.5	-	-	-
Nystatin	-	-	-	-	50	50	50

Conclusions

We report an atom-economical multi-component reaction at room temperature by stirring in the presence of piperidine as catalyst along with methanol as the solvent to synthesize different oxoindoline derivatives SP-201 to SP-221. The results obtained from evaluation makes them promising tools for additional *in vivo* and *in vitro* evaluations for the development of lead with potential antimicrobial activity in the treatment of numerous dieses. Further research and development are in progress in our laboratory in this area**.**

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