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Design, Synthesis and Pharmacological Evaluation of Pyrimidine Fused Indane-1,3-dione Derivatives

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ABSTRACT

Schiff's base of indane-1,3-dione (GS4a-GS4j) were synthesized from pyrimidine derivatives of indane dione. The structures of new compounds are confirmed by Fourier Transform Infrared Spectroscopy (FTIR), Proton Nuclear Magnetic Resonance (^{1}H NMR) and Mass spectral data. Schiff's base and pyrimidine derivatives were evaluated for their analgesic, anti-inflammatory. Amongst the compound tested compound GS4a and GS4b were found to have comparable activity with that of standards. Analyzing the pharmacological properties of both the pyrimidine and Schiff's bases of indane-1,3-dione it was found that Schiff's bases were found to be more potent when compared to that of pyrimidine derivatives.

Keywords: Indane-1,3-dione, Pyrimidine, Schiff's bases, Analgesic, Anti-inflammatory

INTRODUCTION

Indane-1, 3-dione and its derivatives constitute a unique group of compounds and attracted the attention of organic chemist and biologist due to their characteristic features [1,2]. Indane-1,3-dione and pyrimidine derivatives represents one of the most biologically active classes, possessing a wide spectrum of activities various substituted indane-1,3-dione [3-5] and pyrimidine derivatives are associated with diverse pharmacological activities such as, anticoagulant [6], analgesic [7], anti-inflammatory [8,9], anticancer [10,11], antibacterial, antifungal [12,13], psychopharmacological activities [14]. Along with these activities numerous research papers have shown that pyrimidine derivatives have other diverse pharmacological activities such as they act as H_1 -antihistamine [15], as selective type 4-phosphodiesterase inhibitors. Indane-1,3-dione constitute a unique group of compounds due to its 1,3-dicarbonyl nature having specific physicochemical property which offers wide scope of studies in problem of theoretical organic chemistry particularly on the basis of tautomerism, dual reactivity.

In addition to the diverse biological activities of pyrimidine and indane-1,3-dione other heterocycles in association with pyrimidines play an essential role in several biological processes and have a considerable chemical and pharmacological importance. In the view of the facts mentioned above and as part of our initial efforts to discover potentially active new agents, we have synthesized a series of pyrimidine derivatives of indane-1,3-dione and evaluated for its anti-inflammatory, analgesic activities.

MATERIALS AND METHODS

All the reactions were carried out with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Melting points were determined by open capillary tubes and were uncorrected. Fourier Transform Infrared Spectroscopy (FTIR) spectra of the powdered compounds were recorded using ATR on a Bruker FTIR spectrophotometer using Diffuse Reflectance Attachment and are reported in cm^{-1} and ^{1}H NMR spectra were recorded on a Bruker (300 MHz FT NMR) spectrophotometer using Tetramethylsilane (TMS) as an internal reference (Chemical shift represented in δ ppm). Mass spectra were recorded on GC–MS QP5050A System (benchtop quadrupole mass spectrophotometer). Purity of the compounds was checked on TLC plates using silica gel Gas stationary phase and was visualized using iodine vapors or under UV chambers.

Synthetic studies

Procedure for the preparation of 2 -acetyl-1H-indene-1, 3 (2H)-dione (GS1)

2-Acetyl indane-1, 3-dione was prepared as per the procedure given by Enchev et al. [16] Yield: 73.82% (solid); mp. 108-110°C. FTIR (KBr) cm^{-1}: 1740, 1775 (C=O); 3092 (Ar-CH); 2960 (CH_3). ^{1}H NMR ($CDCl_3$, δ ppm): 7.11-7.77 (m, 4H, Ar-H); 2.31 (s, 3H, CH_3); 4.87 (s, 1H, CH). Mass spectra of compound exhibited molecular ion peak at m/z 188 (M^+), 189 (M+1), 190 (M+2).

General procedure for the preparation of compounds (GS2a-GS2j)

Equimolar quantities of 2-acetyl-1*H*-indene-1,3 (2*H*)-dione (0.01 M) and substituted aromatic benzaldehyde (0.01 M) were dissolved in minimum amount of alcohol. Sodium hydroxide solution (0.02 M) was added slowly and the mixture stirred for 2 h until the entire mixture becomes very cloud. Then the mixture was poured slowly into 400 ml of water with constant stirring and kept in refrigerator for 24 h. The precipitate obtained was filtered, washed and recrystallized from ethanol [17].

2-[(2)-3(2-nitrophenyl) prop-2-enoyl]- indane-1,3-dione (GS2a)

Yield: 82.86% (solid); mp 180°C. FTIR (KBr) cm^{-1}: 1735, 1783 (C=O); 3074 (Ar-CH); 1632 (CH=CH); 1345 symm, 1504 asymm (NO_2). ^1H NMR ($CDCl_3$, δ ppm) 4.7 (s, 1H, CH); 6.7 (d, 1H, CH=CH); 7.2 (d, 1H, CH=CH); 6.81-7.89 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 321 (M^+), 322 (M+1), 323 (M+2).

2-[(2)-3(3-nitrophenyl) prop-2-enoyl]-indane-1,3-dione (GS2b)

Yield: 81.63% (solid); mp 164°C. FTIR (KBr) cm^{-1}: 1740, 1778 (C=O); 3089 (Ar-CH); 1637 (CH=CH); 1343 symm, 1508 asymm (NO_2). ^1H NMR ($CDCl_3$, δ ppm) 4.7 (s, 1H, CH); 6.73 (d, 1H, CH=CH); 7.21 (d, 1H, CH=CH); 6.91-7.79 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 321 (M^+), 322 (M+1), 323 (M+2).

2-[(2)-3-(4-nitrophenyl) prop-2-enoyl]- indane-1,3-dione (GS2c)

Yield: 77.87% (solid); mp. 150°C. FTIR (KBr) cm^{-1}: 1742, 1772 (C=O); 3091 (Ar-CH); 1640 (CH=CH); 1346 symm, 1510 asymm (NO_2). ^1H NMR ($CDCl_3$, δ ppm) 4.72 (s, 1H, CH); 6.73 (d, 1H, CH=CH); 7.21 (d, 1H, CH=CH); 7.12-8.13 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 321 (M^+), 322 (M+1), 323 (M+2).

2-[(2)-3-(4-chlorophenyl) prop-2-enoyl]- indane-1,3-dione (GS2d)

Yield: 82.76% (solid); mp. 172°C. FTIR (KBr) cm^{-1}: 1748, 1760 (C=O); 3087 (Ar-CH); 1642 (CH=CH); 735 (C-Cl). ^1H NMR ($CDCl_3$, δ ppm) 4.81 (s, 1H, CH); 6.77 (d, 1H, CH=CH); 7.26 (d, 1H, CH=CH); 7.21-7.98 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 311 (M^+), 312 (M+1), 313 (M+2).

2[(2)-3-[4-(dimethylamino) phenyl] prop-2-enoyl]- indane-1,3-dione (GS2e)

Yield: 70.55% (solid); mp. 169°C. FTIR (KBr) cm^{-1}: 1748, 1776 (C=O); 3130 (Ar-CH); 1641 (CH=CH); 2960 (CH_3). ^1H NMR ($CDCl_3$, δ ppm) 4.81 (s, 1H, CH); 6.89 (d, 1H, CH=CH); 7.17 (d, 1H, CH=CH); 2.89 (s, 6H, 2 × CH_3); 7.41-8.43 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 319 (M^+), 320 (M+1), 321 (M+2).

2-[(2)-3-(4-methoxyphenyl) prop-2-enoyl]- indane-1,3-dione GS2f)

Yield: 76.12% (solid); mp. 82°C. FTIR (KBr) cm^{-1}: 1748, 1776 (C=O); 3130 (Ar-CH); 1641 (CH=CH); 2963 (CH_3). ^1H NMR ($CDCl_3$, δ ppm) 4.75 (s, 1H, CH); 6.88 (d, 1H, CH=CH); 7.19 (d, 1H, CH=CH); 3.14 (s, 3H, CH_3); 6.94-7.89 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 306 (M^+), 307 (M+1), 308 (M+2).

2-[(2)-3-(4-methylphenyl) prop-enoyl]- indane-1,3-dione (GS2g)

Yield: 82.35% (solid); mp. 115°C. FTIR (KBr) cm^{-1}: 1741, 1760 (C=O); 3078 (Ar-CH); 1652 (CH=CH); 2964 (CH_3). ^1H NMR ($CDCl_3$, δ ppm) 4.71 (s, 1H, CH); 6.79 (d, 1H, CH=CH); 7.27 (d, 1H, CH=CH); 2.3 (s, 3H, CH_3); 7.10-7.79 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 290 (M^+), 291 (M+1), 292 (M+2).

2-[(2)-3-(2-hydroxyphenyl) prop-2-enoyl]-1H-indene-1,3(2H)-dione (GS2h)

Yield: 72.45% (solid); mp. 180°C. FTIR (KBr) cm^{-1}: 1735, 1758 (C=O); 3140 (Ar-CH); 1658 (CH=CH); 3573 (O-H). ^1H NMR ($CDCl_3$, δ ppm) 4.81 (s, 1H, CH); 7.32 (d, 1H, CH=CH); 7.85 (d, 1H, CH=CH); 5.6 (s, 1H, OH); 7.23-8.31 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 292 (M^+), 293 (M+1), 294 (M+2).

2-[(2)-3-(4-hydroxy-3-methoxyphenyl) prop-2enoyl]-1H-indene-1,3(2H)-dione (GS2i)

Yield: 80.00% (solid); mp. 134°C. FTIR (KBr) cm^{-1}: 1741, 1767 (C=O); 3070 (Ar-CH); 1648 (CH=CH); 2987 (CH_3); 3533 (O-H). ^1H NMR ($CDCl_3$, δ ppm) 4.71 (s, 1H, CH); 6.88 (d, 1H, CH=CH); 7.13 (d, 1H, CH=CH); 3.4 (s, 3H, CH_3) 5.3 (s, 1H, OH); 6.93-7.41 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 322 (M^+), 323 (M+1), 324 (M+2).

2-[(2E)-3-phenylprop-2-enoyl]-1H-indene-1,3(2H)-dione (GS2j)

Yield: 79.82% (solid); mp. 142°C. FTIR (KBr) cm^{-1}: 1728, 1760 (C=O); 3072 (Ar-CH); 1658 (CH=CH); ^1H NMR ($CDCl_3$, δ ppm) 4.76 (s, 1H, CH); 7.28 (d, 1H, CH=CH); 7.43 (d, 1H, CH=CH); 6.93-7.41 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 322 (M^+), 323 (M+1), 324 (M+2).

General procedure for synthesis of compounds [GS-3(a-j)]

A mixture of the corresponding chalcone (3.16 g, 10 mmol), guanidine hydrochloride (1.8 g, 10 mmol) and sodium hydroxide (5 ml, 60%) was refluxed in ethanol (50 ml) for 10-14 h. The reaction mixture were then poured into cold water and neutralized with dilute hydrochloric acid. The precipitated solid was filtered and washed with water and then recrystalised by using ethanol as a solvent [18].

2 -[2-amino-6-(2-nitrophenyl)pyrimidin-4yl]-1H-indene-1,3(2H)-dione (GS3a)

Yield: 73.45% (solid); mp. 157°C. FTIR (KBr) cm^{-1}: 1735, 1753 (C=O); 3054 (Ar-CH); 1658 (CH=CH); 1356 symm, 1533 asymm (NO_2); 3233, 3314 (NH_2). ^1H NMR ($CDCl_3$, δ ppm) 4.63 (s, 1H, CH); 5.43 (s, 2H, NH_2); 6.62 (s, 1H, CH); 6.84-7.99 (m, 8H, Ar-H).Mass spectra of compound exhibited molecular ion peak at m/z 360 (M^+), 361 (M+1), 362 (M+2).

2-[2-amino-6-(3-nitrophenyl)pyrimidin-4yl]-1H-indene-1,3(2H)-dione (GS3b)

Yield: 81.63% (solid); mp. 164°C. FTIR (KBr) cm^{-1}: 1740, 1778 (C=O); 3089 (Ar-CH); 1343 symm, 1508 asymm (NO_2); 3246, 3328 (NH_2). ^1H NMR ($CDCl_3$, δ ppm) 4.7 (s, 1H, CH); 6.72 (s, 1H, CH); 6.91-7.79 (m, 8H, Ar-H).

Mass spectra of compound exhibited molecular ion peak at m/z 360 (M^+), 361 (M+1), 362 (M+2).

2-2-[2-amino-6-(4-nitrophenyl)pyrimidin-4-yl]-1H-indene-1,3(2H)-dione (GS3c)

Yield: 78.57% (solid); mp. 183°C. (KBr) cm^{-1}: 1740, 1763 (C=O); 3095 (Ar-CH); 3278, 3395 (NH_2); 1336 symm, 1515 asymm (NO_2). ^1H NMR ($CDCl_3$, δ ppm) 4.6 (s, 1H, CH); 5.31 (s, 2H, NH_2); 6.53 (s, 1H, CH); 7.01-7.79 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 360 (M^+), 361 (M+1), 362 (M+2).

2-[2-amino-6-(4-chlorophenyl)pyrimidin-4-yl]-1H-indene-1,3(2H)-dione (GS3d)

Yield: 65.41% (solid); mp. 191ºC. FTIR (KBr) cm^{-1}: 1752, 171763 (C=O); 3093 (Ar-CH); 3267, 3331 (NH_2); 750 (C-Cl). ^1H NMR ($CDCl_3$, δ ppm) 4.55 (s, 1H, CH); 5.31 (s, 2H, NH_2); 6.51 (s, 1H, CH); 6.90-7.63 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 350 (M^+), 351 (M+1), 352 (M+2).

2-{2-amino-6-[4-(dimethylamino)phenyl]pyrimidin-4-yl}-1H-indene-1,3(2H)-dione (GS-3e)

Yield: 78.35% (solid); mp. 165°C. FTIR (KBr) cm^{-1}: 1717, 1742 (C=O); 3126 (Ar-CH); 3267, 3327 (NH_2). ^1H NMR ($CDCl_3$, δ ppm) 4.81 (s, 1H, CH); 5.11 (s, 2H, NH_2); 7.11 (s, 1H, CH); 3.12 (s, 6H, 2 × CH_3); 6.84-7.99 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 358 (M^+), 359 (M+1), 360 (M+2).

2-[2-amino-6-(4-methoxyphenyl)pyrimidin-4-yl]-1H-indene-1,3(2H)-dione (GS3f)

Yield: 76.19% (solid); mp. 134°C. (KBr) cm^{-1}: 1725, 1754 (C=O); 3067 (Ar-CH); 3354, 3398 (NH_2); 1256 (C-O). ^1H NMR ($CDCl_3$, δ ppm) 4.51 (s, 1H, CH); 6.65 (s, 2H, NH_2); 6.24 (s, 1H, CH); 3.83 (s, 1H, CH_3); 7.15-7.89 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 345 (M^+), 346 (M+1), 347 (M+2).

2-[2-amino-6-(4-methylphenyl)pyrimidin-4-yl]-1H-indene-1,3(2H)-dione (GS3g)

Yield: 68.29% (solid); mp. 164°C. FTIR (KBr) cm^{-1}: 1734, 1752 (C=O); 3074 (Ar-CH); 2962 (CH_3); 3246, 3328 (NH_2). ^1H NMR ($CDCl_3$, δ ppm) 4.6 (s, 1H, CH); 6.52 (s, 1H, CH); 2.53 (s, 3H, CH_3) 7.21-8.00 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 329 (M^+), 330 (M+1), 331 (M+2).

2-[2-amino-6-(2-hydroxyphenyl)pyrimidin-4-yl]-1H-indene-1,3(2H)-dione (GS3h)

Yield: 74.88% (solid); mp. 161°C. FTIR (KBr) cm^{-1}: 1715, 1730 (C=O); 3143 (Ar-CH); 3572 (OH); 3236, 3298 (NH_2). ^1H NMR ($CDCl_3$, δ ppm) 4.41 (s, 1H, CH); 6.22 (s, 1H, CH); 5.18 (s, 1H, OH); 7.32-7.91 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 331 (M^+), 332 (M+1), 333 (M+2).

2-[2-amino-6-(4-hydroxy-3-methoxyphenyl)pyrimidin-4-yl]-1H-indene-1,3(2H)-dione (GS3i)

Yield: 72.18% (solid); mp. 154°C. (KBr) cm^{-1}: 1725, 1734 (C=O); 3117 (Ar-CH); 3254, 3398 (NH_2); 1326 (C-O); 3458 (OH). ^1H NMR ($CDCl_3$, δ ppm) 4.81 (s, 1H, CH); 6.65 (s, 2H, NH_2); 6.84 (s, 1H, CH); 2.83 (s, 1H, CH_3); 5.87 (s, 1H, OH); 7.25-8.23 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 361 (M^+), 362 (M+1), 363 (M+2).

2-(2-amino-6-phenylpyrimidin-4-yl)-1H-indene-1, 3(2H)-dione (GS3j)

Yield: 58.35% (solid); mp 121°C. FTIR (KBr) cm^{-1}: 1728, 1758 (C=O); 3060 (Ar-CH); 3316, 3388 (NH_2). ^1H NMR ($CDCl_3$, δ ppm) 4.7 (s, 1H, CH); 6.72 (s, 1H, CH); 5.37 (s, 2H, NH_2); 6.91-7.79 (m, 8H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 315 (M^+), 316 (M+1), 317 (M+2).

General procedure for the synthesis of compounds [GS-4(a-j)]

To a stirred solution of pyrimidine derivatives GS3a-GS3j (0.02 M, 5 g) in methanol (50 ml) containing a glacial acetic acid, (2 ml) *p*-methoxy benzaldehyde (0.02 M) was added and the mixture was refluxed for 6-8 h on a water bath. The separated solvent was distilled off at reduced pressure and resulting solid was collected, dried and crystallized from ethanol to give the Schiff bases GS-4(a-j)' [19].

2-(2-(4-methoxybenzylideneamino)-6-(2-nitrophenyl)pyrimidin-4-yl)-2*H*-indene-1,3-dione. (GS4a)

Yield: 69.82% (solid); mp. 209°C. FTIR (KBr) cm^{-1}: 1737, 1751 (C=O); 3033 (Ar-CH); 2858 (Aliphatic-CH); 1353 symm, 1537 asymm (NO_2); 1657 (C=N) ^1H NMR ($CDCl_3$, δ ppm) 4.72, 7.42, 8.12 (s, 1H, CH); 3.77 (s, 3H, OCH_3), 6.94-8.00 (m, 12H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 478 (M^+), 479 (M+1), 480 (M+2).

2-(2-(4-methoxybenzylideneamino)-6-(3-nitrophenyl)pyrimidin-4-yl)-2H-indene-1,3-dione. (GS4b)

Yield: 71.82% (solid); mp. 221°C. FTIR (KBr) cm^{-1}: 1742, 1767 (C=O); 3053 (Ar-CH); 2908 (Aliphatic-CH); 1359 symm, 1531 asymm (NO_2); 1647 (C=N) ^1H NMR ($CDCl_3$, δ ppm) 4.73, 7.49, 8.21 (s, 1H, CH); 3.64 (s, 3H, OCH_3), 7.14-7.84 (m, 12H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 478 (M^+), 479 (M+1), 480 (M+2).

2-(2-(4-methoxybenzylideneamino)-6-(4-nitrophenyl)pyrimidin-4-yl)-2H-indene-1,3-dione. (GS4c)

Yield: 68.32% (solid); mp. 193°C. FTIR (KBr) cm^{-1}: 1740, 1761 (C=O); 3047 (Ar-CH); 2924 (Aliphatic-CH); 1355 symm, 1540asymm (NO_2); 1645 (C=N). ^1H NMR ($CDCl_3$, δ ppm) 4.53, 7.52, 8.22 (s, 1H, CH); 3.74 (s, 3H, OCH_3), 7.14-7.84 (m, 12H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 478 (M^+), 479 (M+1), 480 (M+2).

2-(2-(4-methoxybenzylideneamino)-6-(4-chlorophenyl)pyrimidin-4-yl)- 2H-indene-1,3-dione. (GS4d)

Yield: 73.11% (solid); mp. 240°C. FTIR (KBr) cm^{-1}: 1741, 1758 (C=O); 3045 (Ar-CH); 2858 (Aliphatic-CH); 755 (C-Cl); 1659 (C=N), 1211 (C-O). ^1H NMR ($CDCl_3$, δ ppm) 4.61, 7.44, 8.21 (s, 1H, CH); 3.67 (s, 3H, OCH_3), 7.14-8.00 (m, 12H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 468 (M^+), 469 (M+1), 470 (M+2).

2-(2-(4-methoxybenzylideneamino)-6-(4-dimethylamino phenyl) pyrimidin-4-yl)-2H-indene-1,3-dione. (GS4e):

Yield: 71.84% (solid); mp. 178°C. FTIR (KBr) cm^{-1}: 1745, 1756 (C=O); 3047 (Ar-CH); 2860 (Aliphatic-CH); 1655 (C=N). ^1H NMR ($CDCl_3$, δ ppm) 4.74, 7.51, 8.22 (s, 1H, CH); 3.62 (s, 3H, OCH_3), 2.85 (s, 6H, $2NCH_3$), 6.98-8.12 (m, 12H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 477 (M^+), 478 (M+1), 479 (M+2).

2-(2-(4-methoxybenzylideneamino)-6-(4-methoxyphenyl phenyl) pyrimidin-4-yl)-2H-indene-1,3-dione. (GS4f)

Yield: 72.23% (solid); mp. 161°C. FTIR (KBr) cm^{-1}: 1742, 1765 (C=O); 3059 (Ar-CH); 2880 (Aliphatic-CH); 1668 (C=N); 1265 (C-O). ^1H NMR ($CDCl_3$, δ ppm) 4.68, 7.95, 8.64 (s, 3H, 3CH); 3.62 (s, 6H, $2OCH_3$), 7.18-8.22 (m, 12H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 447 (M^+), 448 (M+1), 449 (M+2).

2-(2-(4-methoxybenzylideneamino)-6-(4-methyl phenyl) pyrimidin-4-yl)-2H-indene-1,3-dione. (GS4g)

Yield: 64.39% (solid); mp 256°C. FTIR (KBr) cm^{-1}: 1739, 1753 (C=O); 3093 (Ar-CH); 2900 (Aliphatic-CH); 1663 (C=N), 1235 (C-O). ^1H NMR ($CDCl_3$, δ ppm) 4.75, 7.77, 8.35 (s, 3H, 3CH); 2.74 (s, 3H, CH_3), 3.54 (s, 3H, OCH_3), 7.24-8.20 (m, 12H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 449 (M^+), 450 (M+1), 451 (M+2).

2-(2-(4-methoxybenzylideneamino)-6-(2-hydroxyphenyl) pyrimidin-4-yl)-2H-indene-1,3-dione. (GS4h)

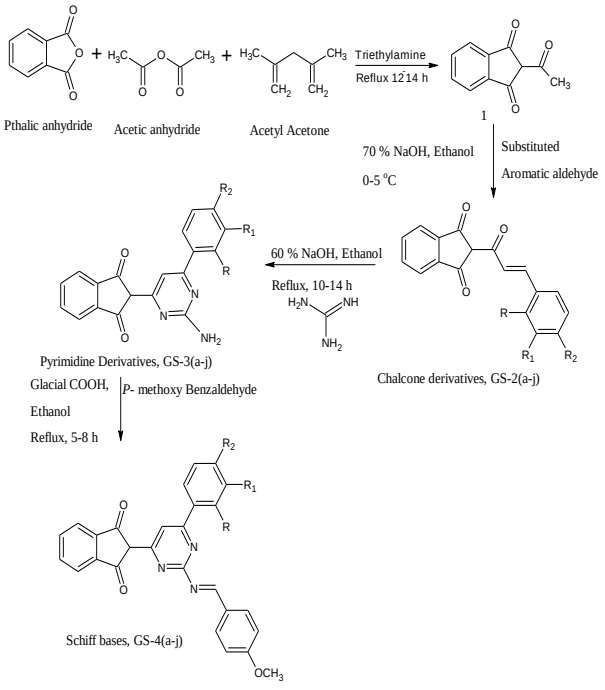
Yield: 70.14% (solid); mp. 184°C. FTIR (KBr) cm^{-1}: 1737, 1761 (C=O); 3059 (Ar-CH); 2892 (Aliphatic-CH); 1665 (C=N); 3341 (O-H); 1265 (C-O). ^1H NMR ($CDCl_3$, δ ppm) 4.67, 7.72, 8.81 (s, 3H, 3CH); 3.51 (s, 3H, OCH_3), 7.21-8.16 (m, 12H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 463 (M^+), 464 (M+1), 465 (M+2).

2-(2-(4-methoxybenzylideneamino)-6-(4-hydroxy-3-methoxyphenyl) pyrimidin-4-yl)-2H-indene-1,3-dione. (GS4i)

Yield: 72.23% (solid); mp. 161°C. FTIR (KBr) cm^{-1}: 1742, 1765 (C=O); 3059 (Ar-CH); 2880 (Aliphatic-CH); 1668 (C=N); 1265 (C-O). ^1H NMR ($CDCl_3$, δ ppm) 4.68, 7.95, 8.64 (s, 3H, 3CH); 3.62 (s, 6H, $2OCH_3$), 7.18-8.22 (m, 12H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 480 (M^+), 481 (M+1), 482 (M+2).

2-(2-(4-methoxybenzylideneamino)-6-phenylpyrimidine-4-yl)-2H-indene-1,3-dione (GS4j)

Yield: 62.63% (solid); mp 177°C. FTIR (KBr) cm^{-1}: 1747, 1756 (C=O); 3021 (Ar-CH); 2892 (Aliphatic-CH); 1657 (C=N). ^1H NMR ($CDCl_3$, δ ppm) 4.74, 7.51, 8.22 (s, 1H, CH); 3.71 (s, 3H, OCH_3), 7.09-8.12 (m, 12H, Ar-H). Mass spectra of compound exhibited molecular ion peak at m/z 434 (M^+), 435 (M+1), 436 (M+2).



Scheme 1: Schematic representation of synthesis of compounds (GS2a-GS4j)

Pharmacological studies

Animal

Swiss Albino mice of either sex weighing 20-25 g and Wistar rat weighing in the range 100-120 g were obtained from Bioneeds, Bangalore. All the animals were housed under standard ambient conditions of temperature (25 ± 2°C) and relative humidity of 50 ± 5%. A 12:12 h light: dark cycle was maintained. All the animals were allowed to have free access to water and standard palletized laboratory animal diet 24 h prior to pharmacological studies.

All the experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) of College, Bangalore, constituted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Table 1: Physicochemical characterization of compounds (GS1a-GS4j)

S. No.	Comp. code	R	0	0	Mol. Formula	Mol. Wt. (g)	M.P.(°C)*	% yield	R_f**
1	GS-2a	NO_2	H	H	$C_{18}H_{11}NO_5$	321.28	180	82.86	0.7
2	GS-2b	H	NO_2	H	$C_{18}H_{11}NO_5$	321.28	164	81.63	0.71
3	GS-2c	H	H	NO_2	$C_{18}H_{11}NO_5$	321.28	150	77.87	0.84
4	GS-2d	H	H	Cl	$C_{18}H_{11}ClO_3$	310.73	172	82.76	0.68
5	GS-2e	H	H	$N(CH_3)_2$	$C_{20}H_{17}NO_3$	319.35	169	70.55	0.73
6	GS-2f	H	H	OCH_3	$C_{19}H_{14}O_4$	306.31	82	76.12	0.8
7	GS-2g	H	H	CH_3	$C_{19}H_{14}O_3$	290.31	115	82.35	0.71
8	GS-2h	OH	H	H	$C_{18}H_{12}O_4$	292.28	180	72.45	0.82
9	GS-2i	H	OCH_3	OH	$C_{19}H_{14}O_5$	322.31	134	80	0.75
10	GS-2j	H	H	H	$C_{18}H_{12}O_3$	276.28	142	79.82	0.9
11	GS-3a	NO_2	H	H	$C_{19}H_{12}N_4O_4$	360.32	157	73.45	0.72
12	GS-3b	H	NO_2	H	$C_{19}H_{12}N_4O_4$	360.32	172	76.66	0.77
13	GS-3c	H	H	NO_2	$C_{19}H_{12}N_4O_4$	360.32	183	69.88	0.76
14	GS-3d	H	H	Cl	$C_{19}H_{12}ClN_3O_4$	349.77	191	81.52	0.82
15	GS-3e	H	H	$N(CH_3)_2$	$C_{21}H_{18}N_4O_2$	358.39	165	75.86	0.68
16	GS-3f	H	H	OCH_3	$C_{20}H_{15}N_3O_3$	345.35	134	62.95	0.75
17	GS-3g	H	H	CH_3	$C_{20}H_{15}N_3O_2$	329.35	179	68.29	0.86
18	GS-3h	OH	H	H	$C_{19}H_{13}N_3O_3$	331.32	161	74.88	0.81
19	GS-3i	H	OCH_3	OH	$C_{20}H_{15}N_3O_4$	361.35	154	72.19	0.74
20	GS-3j	H	H	H	$C_{19}H_{13}N_3O_2$	315.32	121	58.35	0.78
21	GS-4a	NO_2	H	H	$C_{27}H_{18}N_4O_5$	478.45	209	69.82	0.73
22	GS-4b	H	NO_2	H	$C_{27}H_{18}N_4O_5$	478.45	221	71.51	0.75
23	GS-4c	H	H	NO_2	$C_{27}H_{18}N_4O_5$	478.45	193	68.32	0.68
24	GS-4d	H	H	Cl	$C_{27}H_{18}ClN_3O_3$	467.9	240	73.11	0.61
25	GS-4e	H	H	$N(CH_3)_2$	$C_{29}H_{24}N_4O_3$	476.5	178	71.84	0.81
26	GS-4f	H	H	OCH_3	$C_{28}H_{21}N_3O_3$	447.48	161	72.23	0.79
27	GS-4g	H	H	CH_3	$C_{27}H_{19}N_3O_4$	449.45	256	64.39	0.85
28	GS-4h	OH	H	H	$C_{28}H_{21}N_3O_4$	463.48	184	70.14	0.91
29	GS-4i	H	OCH_3	OH	$C_{28}H_{21}N_3O_5$	479.48	239	68.46	0.76
30	GS-4j	H	H	H	$C_{27}H_{19}N_3O_3$	433.45	177	62.63	0.88

Table 2: Analgesic activity of compounds (GS3a-GS4j)

Compounds	Reaction time (s) after drug administration (Mean ± SEM[a])			Percent increase in reaction time		
	30 min	60 min	90 min	30 min	60 min	90 min
GS-3a	5.99 ± 0.07	6.80 ± 0.06	7.28 ± 0.02	15.55^{**}	23.12^{**}	27.01^{**}
GS-3b	5.12 ± 0.15	5.76 ± 0.16	6.27 ± 0.09	8.62^{**}	14.48^{**}	19.25^{**}
GS-3c	5.50 ± 0.13	6.46 ± 0.09	6.67 ± 0.09	11.45^{**}	20.38^{**}	22.40^{**}
GS-3d	5.56 ± 0.35	6.26 ± 0.20	6.71 ± 0.19	11.80^{**}	18.34^{**}	22.62^{**}
GS-3e	5.01 ± 0.11	5.63 ± 0.17	6.18 ± 0.05	6.23^{*}	12.03^{**}	17.23^{**}
GS-3f	5.06 ± 0.16	5.64 ± 0.19	6.16 ± 0.17	6.00^{*}	11.44^{**}	16.43^{**}
GS-3g	5.23 ± 0.08	6.02 ± 0.16	6.53 ± 0.15	8.20^{**}	15.44^{**}	20.31^{**}
GS-3h	4.91 ± 0.09	5.47 ± 0.14	5.76 ± 0.07	4.48^{ns}	9.75^{**}	12.54^{**}
GS-3i	4.51 ± 0.15	4.73 ± 0.12	5.05 ± 0.13	3.06^{ns}	5.13^{ns}	8.04^{**}
GS-3j	4.95 ± 0.12	5.01 ± 0.11	5.47 ± 0.14	5.02^{*}	5.65^{ns}	9.93^{**}
GS-4a	6.10 ± 0.11	6.87 ± 0.07	7.31 ± 0.05	16.52^{**}	23.74^{**}	27.87^{**}
GS-4b	5.12 ± 0.15	6.05 ± 0.16	6.45 ± 0.04	8.62^{**}	17.21^{**}	20.91^{**}
GS-4c	5.67 ± 0.12	6.63 ± 0.07	6.88 ± 0.04	13.08^{**}	22.00^{**}	24.33^{**}
GS-4d	5.64 ± 0.24	6.33 ± 0.17	6.81 ± 0.13	12.61^{**}	19.02^{**}	23.54^{**}
GS-4e	5.11 ± 0.16	5.71 ± 0.08	6.06 ± 0.04	7.18^{**}	12.80^{**}	16.10^{**}
GS-4f	5.16 ± 0.16	5.82 ± 13.1	6.25 ± 0.20	6.89^{**}	13.168^{**}	17.25^{**}
GS-4g	5.33 ± 0.11	6.16 ± 0.06	6.61 ± 0.11	9.00^{**}	16.81^{**}	21.00^{**}
GS-4h	5.01 ± 0.07	5.53 ± 0.09	5.94 ± 0.08	5.44**	10.38**	14.20**
GS-4i	4.61 ± 0.14	4.88 ± 0.13	5.10 ± 0.08	3.95^{ns}	5.91^{ns}	8.55**
GS-4j	4.97 ± 0.07	5.22 ± 0.16	5.46 ± 0.13	5.24*	7.62**	9.84**
Diclofenac	6.26 ± 0.13	7.27 ± 0.07	8.02 ± 0.08	18.20**	27.59**	34.62**
Control	4.32 ± 0.049	4.47 ± 0.087	4.49 ± 0.091	-	-	-

ANOVA followed by Dunnett's t-test for multiple comparisons. $P < 0.05$ (*) and $P < 0.01$ (**) were taken as significant.a=Standard Error Mean; ns=non-significant

Preparation of test compounds

After suspending the test compounds in 1.0% aqueous solution of Sodium Carboxymethyl Cellulose (SCMC), test samples were administered to test animals orally. The positive and negative control group animals received the same experimental handling as those of the test groups except that the drug treatment, control group animals received only appropriate volumes of vehicle and of the reference drug, diclofenac sodium, respectively.

Table 3: Anti-inflammatory activity (*in vivo*) of compounds (GS3a-GS4j)

Compounds	Mean Volume in (ml) after drug treatment (Mean ± SEM[a])			Anti-inflammatory activity (% inhibition)		
	1 h	2 h	3 h	1 h	2 h	3 h
GS-3a	1.00 ± 0.063	1.10 ± 0.032	1.14 ± 0.014	31.78**	37.84**	40.70**
GS-3b	1.23 ± 0.017	1.41 ± 0.051	1.43 ± 0.026	16.51**	20.28**	25.41**
GS-3c	0.98 ± 0.015	1.04 ± 0.042	1.07 ± 0.037	33.25**	41.22**	44.25**
GS-3d	1.10 ± 0.022	1.20 ± 0.014	1.24 ± 0.021	25.11**	32.11**	35.52**
GS-3e	1.19 ± 0.006	1.30 ± 0.015	1.33 ± 0.018	18.77**	26.38**	30.94**
GS-3f	1.36 ± 0.029	1.57 ± 0.045	1.66 ± 0.029	7.35^{ns}	11.07**	13.56**
GS-3g	1.34 ± 0.045	1.55 ± 0.036	1.63 ± 0.048	8.71*	13.99**	15.38**
GS-3h	1.42 ± 0.009	1.68 ± 0.011	1.77 ± 0.015	3.61^{ns}	5.25^{ns}	7.95**
GS-3i	1.43 ± 0.038	1.72 ± 0.033	1.82 ± 0.016	2.82^{ns}	3.09^{ns}	5.61^{ns}
GS-3j	1.35 ± 0.042	1.52 ± 0.042	1.64 ± 0.045	7.35^{ns}	8.14**	14.77**
GS-4a	0.97 ± 0.48	1.05 ± 0.03	1.08 ± 0.03	34.16**	40.46**	43.90**
GS-4b	1.21 ± 0.02	1.35 ± 0.03	1.39 ± 0.04	17.64**	2.47**	27.83**
GS-4c	0.95 ± 0.01	1.00 ± 0.03	1.04 ± 0.03	35.29**	43.66**	45.72**
GS-4d	1.07 ± 0.04	1.18 ± 0.03	1.18 ± 0.02	26.80**	33.52**	38.72**
GS-4e	1.17 ± 0.03	1.26 ± 0.03	1.32 ± 0.04	20.58**	28.73**	31.11**
GS-4f	1.34 ± 0.04	1.49 ± 0.05	1.57 ± 0.04	8.48^{ns}	15.58**	18.49**
GS-4g	1.30 ± 0.06	1.51 ± 0.03	1.59 ± 0.03	11.42*	14.55**	17.11**
GS-4h	1.38 ± 0.05	1.65 ± 0.03	1.75 ± 0.02	5.88^{ns}	6.85^{ns}	8.98*
GS-4i	1.39 ± 0.02	1.67 ± 0.03	1.78 ± 0.01	5.09^{ns}	5.91^{ns}	7.26*
GS-4j	1.32 ± 0.05	1.50 ± 0.03	1.61 ± 0.05	10.40^{ns}	15.02**	16.16**
Indomethacin	0.90 ± 0.02	0.93 ± 0.02	0.97 ± 0.00	38.57**	47.51**	49.42**
Control	1.47 ± 0.02	1.77 ± 0.02	1.92 ± 0.02	-	-	-

ANOVA followed by Dunnett's t-test for multiple comparisons. P < 0.05 (*) and P < 0.01 (**) were taken as Significant. a= Standard Error Mean; ns=non-significant

Anti-inflammatory activity

Anti-inflammatory activity was evaluated using the well-known carrageenan induced rat paw oedema model of winter et al. [20] using groups of six animals each. A freshly prepared aqueous suspension of carrageenan (1.0% w/v, 0.1 ml) was injected in the subplanter region of right hind paw of each rat. One group was kept as control and the animals of the other group were pretreated with the test drugs, 1 h before the carrageenan treatment. The volume was measured before and after carrageenan treatment at the 30 min. interval with the help of digital plethysmometer (Panlab LE 7500) [21,22].

Analgesic activity

The analgesic activity was evaluated using the Hot plate method [23]. Percent increase in reaction time is calculated using the formula:

$$PAA=[T_2-T_1/10-T_1]$$

Where, PAA=Percent Analgesic Activity, T_2=Reaction time (S) before treatment, T_1=Reaction time (S) after treatment

RESULTS AND DISCUSSION

Chemistry

The synthetic route used to synthesize title compounds is outline in Scheme 1. 2-acetyl-1*H*-indene-1, 3 (2*H*)-dione (1), the starting material, was prepared according to the method reported in the literature, using 2-benzofuran-1,3-dione, petane-2,4-dione and acetic anhydride. Chalcone derivatives [GS-2(a-j)] was prepared by Claisen-Schmidt condensation reaction of 2-acetyl-1*H*-indene-1,3 (2*H*)-dione (GS1) with substituted heterocyclic aldehyde followed by treatment with guanidine hydrochloride in ethanol as a solvent and then obtained 2-[2-amino-6- pyrimidin-4yl]-1*H*-indene-1, 3(2*H*)-dione [GS-3(a-j)] derivatives were prepared. Various Schiff bases [GS-4(a-j)] were prepared in very good yields by treatment of 2-[2-amino-6- pyrimidin-4yl]-1*H*-indene-1,3(2*H*)-dione [GS-3(a-j)] with *p*-methoxy benzaldehyde in ethanol by adding 2-3 drops of glacial acetic acid. The progress of the reaction was being monitored by TLC on silica-G (Merck) coated glass plates, visualized by iodine vapor. Physicochemical data of the IR, NMR and mass spectral data confirmed the formation of the final compound. These results will be reported in due course.

The FT-IR spectra of the pyrimidine derivatives [GS-3(a-j)]exhibited very similar feature and showed the expected bands for the characteristic groups which are present in compounds such as C-H, C=N and the $–NH_2$ stretching is an evidence of ring closure and another specific stretch for three aromatic rings in the range of 3040-3130. The pyrimidine derivatives [GS-3(a-j)] and Schiff bases [GS-4(a-j)] showed C=O stretching band in the range 1680-1760. The Schiff bases [GS-4(a-j)] showed disappearance of $–NH_2$ stretching is an evidence of Schiff base formation. In the proton NMR spectral data, all protons were seen according to the expected chemical shift and integral values.

The aromatic protons appeared as multiplet peaks within the range 6.7-8.0 δ ppm. The ^{1}H NMR spectra of compounds [GS-3(a-j)]and [GS-4(a-j)]displayed singlet around 6.5 and 7.5 δ ppm due to C-H respectively and one additional broad singlet due to $–NH_2$ which was observed in pyrimidine derivatives that disappeared in Schiff base indicating formation of Schiff base. The detailed results of various physicochemical studies are presented in Table 1.

Pharmacology

In the pharmacological studies, we have investigated analgesic and anti-inflammatory activities of pyrimidine derivatives [GS-3(a-j)] and Schiffs base derivatives (GS4a-GS4j).

Analgesic activity

The analgesic activities of the compounds were studied by using hot-plate method in mice. The analgesic activity was evaluated at equimolar doses equivalent to 20 mg/kg orally (Diclofenac) body weight. These compounds exhibited an important analgesic profile measured by the classical eddy's hot plate method. From the results of eddy's hot plate method, it was noticed that all compounds exhibited significant analgesic activity of synthesized compound which is summarized in Table 2.

The investigation of analgesic screening revealed that some of the tested compounds showed moderate to good analgesic activity particularly the compounds GS3a (27.01%), GS3c (22.40%), GS3d (22.62%) from pyrimidine series and GS4a 27.87, GS4c (24.33%), GS4d (23.54%) from Schiff's base series was found to comparable activity with that of Diclofenac sodium (34.65%). This could be due to the availability of electron withdrawing groups (-NO_2 and Cl).

Anti-inflammatory activity

Anti-inflammatory activity of the synthesized compounds was evaluated by carrageenan induced rat paw oedema model, at equimolar doses, to that of 20 mg/kg orally of indomethacin. Subplantar injection of 0.1 ml, 1% carrageenan produced increase in paw volume (oedema) in all the animals of various groups. The onset of action was evident from 1 h in various test groups. The significant reduction ($P < 0.01$) of rat paw oedema was observed by most of the test compounds at 3 h compared to control group.

All of the newly obtained compounds GS3a-GS3j and GS-4(a-j) were tested for *in vivo* anti-inflammatory activity. Compared to the standard, indomethacin, they have shown acceptable anti-inflammatory activity. *In vivo* anti-inflammatory activity of compounds is summarized in Table 3. The compound GS-3a (40.70%), GS-3c (44.25%) from pyrimidine series and GS-4a (40.46%), GS-4c (45.72%) from Schiff's base was found to have comparable activity as that of standard drug indomethacin (49.52%). While others having weak to moderate activity.

CONCLUSION

Various pyrimidine derivatives of indane-1, 3-dione was synthesized and screened for analgesic and anti-inflammatory activities. Most compounds exhibited significant mentioned activities. Analgesic and anti-inflammatory activity screening indicated that some of the tested compounds GS3a, GS3c, GS4a and GS4c showed good analgesic and anti-inflammatory activities. Compounds GS3d and GS4d showed moderate analgesic activities and anti-inflammatory. The results revealed that substitution of a *p*-nitrophenyl and *p*-chlorophenyl group at sixth position of a pyrimidine ring produced an increase in the analgesic and anti-inflammatory activities. Increase in the analgesic and an anti-inflammatory activity is observed for the compounds after conversion of pyrimidine derivatives (GS3a-GS-3j) into Schiff base derivatives (GS4a-GS4j). Decrease in activity is observed when the substitution of a *p*-methylphenyl, *p*-methoxyphenyl groups at sixth position of pyrimidine ring. Thus it was concluded that among the [GS-3(a-j)] series, analgesic and anti-inflammatory activities decrease with the introduction of electron releasing groups.

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