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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and anti-inflammatory activity of 1,2-3-substituted 2a1,4,5-triazacyclopenta[cd]indene derivatives

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Abstract

The present study reports the synthesis of 1,2-3-substituted-2a1,4,5-triazacyclopenta[cd]indene derivatives. The synthetic methodology includes some of the prominent reaction steps as specified in sequence (i) Bromination of acetophenones (ii) Condensation of 2-bromo-1-(substituted phenyl) ethanone derivatives with 2-aminopyrimidine, and (iii) Coupling of imidazo[1,2-a]pyrimidine derivatives with 1,2-diaryl/diaklylethynes. The structures of the newly synthesized derivatives have been determined by ^{1}H NMR, ^{13}C NMR, LC-MS, and IR spectral analysis. Furthermore, these derivatives were screened for their preliminary anti-inflammatory activities using Carrageenan induced paw edema test method. These promising screening results suggested a huge potential for the molecular diversity from present compounds that can be inflated to better lead candidates.

Keywords Acyl bromides · 2-Aminopyrimidine · Anti-inflammatory · Synthesis · Imidazo[1 · 2-a] pyrimidines

Introduction

Over the past few years there is considerable interest in the synthesis and pharmacological studies of heteroaromatic organic compounds like imidazopyridines, imidazopyrimidines, etc since they possess promising biological activity like anticancer activity (Kim et al. 2011; Yoshiyuki et al. 2009). Synthesis and construction of fused poly-cyclic heteroaromatic compounds via transition-metal-catalyzed C–H bond functionalization has become an increasingly important tool in recent years as this process provides a simple, direct, and atom-economic access to π-conjugated heteroaromatic molecules (Sanjay et al. 2016). These polycyclic heteroaromatic compounds attracted considerable attention due to their biological and pharmacological activities (Sanjay et al. 2015, 2016). Imidazo [1,2-a]pyridines and alkynes have been used as substrates for the preparation of poly-cyclic heteroaromatic compounds in the presence of Palladium catalyst and in the presence of oxidizing agents (Xuesen Li et al. 2015). Imidazopyridines also exhibit widest range of biological activities such as anti helminthic, anti fungal (Michael and Aino 1972), anti tumor (William et al. 1991), anti viral (Song et al. 2015), anti-bacterial (Rival et al. 1992), anti protozoal, anti-pyretic, and anti anxiety agents (Avik et al. 2015; Lucyna 2015). Closest to the above fused heterocycle motifs are imidazopyrimidines that are found in several natural, as well as synthetic biologically active molecules (Fewell and Woolford 1999). Imidazopyrimidine derivatives were proved to have several properties like anti-bacterial (Rival et al. 1992), anti fungal (Rival et al. 1991), analgesic, anti-inflammatory (Simon et al. 2006), (Gaozhi et al. 2013), anti-pyretic, and anti-convulsant activities (Ulloora et al. 2013).

Inspired by the above mentioned reaction sequence, we report herein the synthesis and anti-inflammatory activity of some new imidazo (1,2-a) pyrimidine derivatives utilizing 2-amino-pyrimidine and alkyl/aryl alkynes as starting materials followed by further derivatizing to new class of 1,2,3-substituted-2a1,4,5-triazacyclopenta[cd]indene compounds **25**–**36**. To the best of our knowledge, these new derivatives have not been reported in the literature so far.

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Experimental section

Materials and methods

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and were used without further purification. Reactions were monitored by TLC, performed on silica-gel glass plates containing 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. ^{1}H and ^{13}C NMR spectra were recorded on Bruker, Bruker UXNMR/XWIN-NMR (500 MHz, 400 MHz, 300 MHz) instrument. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electro thermal melting point apparatus, and are uncorrected. The LCMS purity of the final compounds were determined under the following optimized condition using "**Column**: KINETEX-1.7 µ XB-C18 100 A (2.1 × 50 mm); **Mobile phase A**: 0.05% FA in H_2O; **Mobile phase B**: 0.05% FA in ACN; T/%A: 0/97, 0.3/97, 3.2/2, 4.8/2, 5/97, 5.10/97; **Flow rate**: 0.6 mL/min, Temp: 35 °C.

General procedure for synthesis of α-haloketones (7–12)

To a solution of acetophenones **1**–**6** (16.65 mmol) in 2-Me-tetrahydrofuran (20 mL), copper(II)bromide (19.98 mmol) was added (Raghunath et al. 2015). The reaction mixture was allowed to stir at room temperature for 24 h. After completion of the reaction (monitored by TLC), reaction mixture was filtered off. The filtrate containing the 2-bromo-1-phenylethanones **7**–**12** was taken to the next step without isolation. However, to check the purity of the formed phenacyl bromides, two representative compounds (**8** and **10**) were isolated in standard procedure by evaporating the solvent under vacuum and confirmed by spectral analysis (^{1}H NMR, Mass, and HPLC). As all the derivatives were pure by TLC, they were preceded to next step without purification/isolation.

General procedure for synthesis of imidazo[1,2-a] pyrimidines (14–19)

To the above filtrate, containing 2-bromo-1-phenylethanones **7**–**12** (4.16 g, 21.03 mmol), sodium bicarbonate (8.83 g, 105.15 mmol), additional quantity of 2-Me-THF (10 mL), and 2-aminopyrimidine **13** (2 g, 21.03 mmol) were added and heated to 85 °C for 10 h in a sealed tube. After completion of the reaction (monitored by TLC), the mixture was poured into ice-water (30 mL) with vigorous stirring and the organic layer i.e., 2-Me-tetrahydrofuran containing was separated, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to obtain the corresponding 2-phenylimidazo[1,2-a]pyrimidine **14**–**19**. Two of the representative derivatives (**15** and **17**) were characterized by ^{1}H NMR, Mass and HPLC for purity and remaining all isolated compounds were directly utilized in the next without further purification.

General procedure for the synthesis of 1,2-3-substituted 2a1,4,5-triazacyclopenta[cd]indene derivatives (25–36)

To a stirred solution of DMF (1 mL):PEG-1500 (1 g) in a sealed tube was added sequentially 2-phenylimidazo[1,2-*a*] pyridine **14**–**19** (100 mg, 0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), $Cu(OAc)_2$ (0.04 mmol), 1,2-diphenylethynes **20**–**24** (0.3 mmol) and TBAB (0.2 mmol) (Sanjay et al. 2016). The reaction mixture was heated to 90 °C for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with aqueous NH_4Cl and extracted with isopropylacetate (10 mL × 3). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum and the crude product was purified by chromatography on silica-gel to afford the desired 1,2-3-substituted 2a^{1},4,5-triazacyclopenta[cd]indene derivatives **25**–**34**. The yields of the products varied between 61–82%.

2-Bromo-2′-methoxyacetophenone (8)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, $J_1 = 1.6$ Hz, $J_2 = 7.6$ Hz, 1H, H-2), 7.52 (dd, $J_1 = 2.0$ Hz, $J_2 = 7.6$ Hz, 1H, H-6), 7.06 – 6.98 (m, 2H, H-1, H-3), 4.61 (s, 2H, H-8), 3.94 (s, 3H, H-12). *m/z* (CI): 229.0 (M + 1, 100%). HPLC: 99.2% [Column: Inertsil ODS 3 V 250 × 4.6 mm, 5 µ; mobile phase: Acetonitrile:Water (50:50, v/v); Flow rate: 0.6 mL/min; Method: Isocratic flow rate].

3-(2-Bromoacetyl)benzonitrile (10)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H, H-4), 8.22 (d, J = 8.0 Hz, 1H, H-6), 7.90 (d, J = 7.6 Hz, 1H, H-2), 7.66 (t, J = 7.6 Hz, 1H, H-1), 4.42 (s, 2H, H-8). *m/z* (CI): 225.2 (M + 1, 100%). HPLC: 99.7% [Column: Inertsil ODS 3 V 250 × 4.6 mm, 5 µ; mobile phase: Acetonitrile:Water (50:50, v/v); Flow rate: 0.6 mL/min; Method: Isocratic flow rate].

2-(2-Methoxyphenyl)imidazo[1,2-a]pyrimidine (15)

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.30 (d, $J = 5.2$ Hz, 1H, H-1), 8.98 (dd, $J_1 = 1.6$ Hz, $J_2 = 4.0$ Hz, 1H, H-3), 8.71

(s, 1H, H-7), 8.05 (dd, $J_1 = 1.6$ Hz, $J_2 = 7.6$ Hz, 1H, H-15), 7.61 (dd, $J_1 = 4.4$ Hz, $J_2 = 6.8$ Hz, 1H, H-2), 7.56-7.52 (m, 1H, H-13), 7.30 (d, $J = 8.0$ Hz, 1H, H-12), 7.21–7.17 (m, 1H, H-14), 4.02 (s, 3H, H-17). *m/z* (CI): 226.0 (M + 1, 100%). HPLC: 99.9% [Column: Inertsil ODS 3 V 250 × 4.6 mm, 5 µ; mobile phase: Acetonitrile:Water (50:50, v/v); Flow rate: 0.6 mL/min; Method: Isocratic flow rate].

3-(Imidazo[1,2-a]pyrimidin-2-yl)benzonitrile (17)

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.00 (d, $J = 2.0$ Hz, 1H, H-1), 8.58 (dd, $J_1 = 2.0$ Hz, $J_2 = 4.0$ Hz, 1H, H-3), 8.53 (s, 1H, H-7), 8.44 (t, $J = 1.2$ Hz, 1H, H-15), 8.35 (td, $J_1 = 1.2$ Hz, $J_2 = 8.0$ Hz, 1H, H-13), 7.84–7.81 (m, 1H, H-12), 7.69 (t, $J = 7.6$ Hz, 1H, H-2), 7.10 (d, $J = 4.4$ Hz, 1H, H-11). *m/z* (CI): 221.1 (M + 1, 100%). HPLC: 99.3% [Column: Inertsil ODS 3 V 250 × 4.6 mm, 5 µ; mobile phase: Acetonitrile:Water (50:50, v/v); Flow rate: 0.6 mL/min; Method: Isocratic flow rate].

1,2,3-Triphenyl-2a1,4,5-triazacyclopenta[cd]indene (25)

Yellow solid; Yield: 76%; mp: 198-200 °C; IR (KBr) ν_{max}: 3051, 2920, 1708, 1537, 1046, 818, 717 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.05 (d, $J = 5.4$ Hz, 1H, H-1), 7.93–7.89 (m, 3H, H-2, 13 and 17), 7.48-7.28 (m, 13H, H-14-16, H-20-29); ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.1 (C-1), 147.5 (C-3), 147.2 (C-5), 136.0 (Ph-C), 134.9 (Ph-C), 133.2 (C-10), 132.8 (C-11), 132.7 (Ph-C), 130.65 (Ph-C), 130.14 (Ph-C), 130.0 (Ph-C), 129.7 (Ph-C), 128.9 (Ph-C), 128.8 (Ph-C), 128.5 (Ph-C), 128.4 (Ph-C), 127.4 (Ph-C), 108.19 (Ph-C); LC-MS: 88%; *m/z* (CI): 372.33 (M + H, 100%).

3-(2-Methoxyphenyl)-1,2-diphenyl-2a1,4,5-triazacyclopenta[cd]indene (26)

Bright yellow solid; Yield: 72%; mp: 259-266 °C; IR (KBr) ν_{max}: 2956, 2852, 1897, 1719, 1406, 1171, 918 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6):δ 9.03 (d, $J = 6.0$ Hz, 1H, H-1), 8.08 (d, $J = 5.2$ Hz, 1H, H-2), 7.97 (dd, $J_1 = 1.6$ Hz, $J_2 = 7.6$ Hz, 1H, H-13), 7.51 (t, $J = 8.8$ Hz, 1H, H-15), 7.43–7.22 (m, 10H, H-20-29), 7.13 (t, $J = 7.2$ Hz, 1H, H-14), 6.9 (d, $J = 8.4$ Hz, 1H, H-16), 2.8 (s, 3H, H-31); ^{13}C NMR (400 MHz, DMSO-d_6): δ 156.1 (C-1), 152.4 (C-3), 147.0 (Ph-C), 146.6 (Ph-C), 135.6 (Ph-C), 134.0 (Ph-C), 133.0 (Ph-C), 132.4 (Ph-C), 132.1 (Ph-C), 131.6 (Ph-C), 129.67 (Ph-C), 129.62 (Ph-C), 128.8 (Ph-C), 128.4 (Ph-C), 128.29 (Ph-C), 127.5 (Ph-C), 125.9 (Ph-C), 123.4 (Ph-C), 122.0 (Ph-C), 120.4 (Ph-C), 110.7 (Ph-C), 108.4 (Ph-C), 53.4 (-OCH_3); LCMS: 99%; *m/z* (CI): 402.4 (M + H 100%).

1,2-Bis(4-fluorophenyl)-3-(2-methoxyphenyl)-2a1,4,5-triazacyclopenta[cd]indene (27)

Yellow solid; Yield: 78%; mp: 95-99 °C; IR (KBr) ν_{max}: 3057, 2923, 1705, 1603, 1042, 839, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.03 (d, $J = 5.1$ Hz, 1H, H-1), 8.15 (dd, $J_1 = 1.2$ Hz, $J_2 = 7.5$ Hz, 1H, H-13), 7.79 (d, $J = 5.7$ Hz, 1H, H-2), 7.5-7.26 (m, 5H, H-15,20,24,25,29), 7.2–7.09 (m, 3H, 21,23,14), 7.0–6.93 (m, 2H, H-26,28), 6.78 (d, $J = 8.4$ Hz, 1H, H-16), 3.01 (s, 3H, H-31); ^{13}C NMR (300 MHz, $CDCl_3$): δ 164.4 (C-1), 163.9 (C-3), 161.1 (C-5), 160.6 (Ph-C), 156.3 (Ph-C), 153.4 (Ph-C), 147.3 (Ph-C), 146.8 (Ph-C), 135.2 (Ph-C), 134.9 (Ph-C), 132.7 (Ph-C), 132.3 (Ph-C), 132.0 (Ph-C), 131.9 (Ph-C), 131.6 (Ph-C), 131.4 (Ph-C), 129.98 (Ph-C), 129.94 (Ph-C), 128.8 (Ph-C), 125.3 (Ph-C), 123.8 (Ph-C), 122.3 (Ph-C), 120.98 (Ph-C), 116.26 (Ph-C), 115.9 (Ph-C),115.5 (Ph-C), 115.2 (Ph-C), 110.1 (Ph-C), 107.5 (Ph-C), 53.6 (-OCH_3); LC-MS: 90%; *m/z* (CI): 438.4 (M + H, 100%).

Dimethyl 3-(2-methoxyphenyl)-2a1,4,5-triazacyclopenta[cd]indene-1,2-dicarboxylate (28)

Yellow solid; Yield: 74%; mp: 175-180 °C; IR (KBr) ν_{max}: 3546, 2864, 1641, 1535, 1459, 1091, 980, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):δ 9.04 (m, 1H, H-1), 8.34 (d, $J = 6.8$ Hz, 1H, H-19), 8.17 (d, $J = 5.2$ Hz, 1H, H-2), 7.56 (t, $J = 7.2$ Hz, 1H, H-21), 7.19 (t, $J = 7.6$ Hz, 1H, H-20), 7.09 (d, $J = 8.4$ Hz, 1H, H-22), 4.00 (s, 3H, H-26), 3.97 (s, 3H, H-27), 3.88 (s, 3H, H-25); ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.2 (C-1), 164.1 (C-3), 163.03 (Ph-C), 157.5 (C-5), 148.5 (Ph-C), 133.5 (Ph-C), 133.4 (Ph-C), 132.5 (Ph-C), 130.6 (Ph-C), 121.6 (Ph-C), 116.1(Ph-C), 111.4 (Ph-C), 110.8 (Ph-C), 56.15 (-OCH_3), 52.8 (-OCH_3), 52.3 (-OCH_3); LC-MS: 95.4%; *m/z* (CI): 366 (M + H, 100%).

Dimethyl 3-(4-methoxyphenyl)-2a1,4,5-triazacyclopenta[cd]indene-1,2-dicarboxylate (29)

Bright yellow solid; Yield: 70%; mp: 183-185 °C; IR (KBr) ν_{max}: 3567, 2853, 1604, 1088, 972, 813 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (d, $J = 5.6$ Hz, 1H, H-1), 8.25 (d, $J = 8.8$ Hz, 2H, H-19,23), 8.11 (d, $J = 6.0$ Hz, 1H, H-2), 7.09 (d, $J = 8.8$ Hz, 2H, H-20,22), 4.12 (s, 3H, H-26), 4.03 (s, 3H, H-27), 3.92 (s, 3H, H-25); ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.3 (C-1), 163.2 (C-3), 163.0 (C-5), 160.9 (Ph-C), 149.0 (Ph-C), 148.7 (Ph-C), 133.0 (Ph-C), 131.0 (Ph-C), 129.0 (Ph-C), 124.0 (Ph-C), 120.4 (Ph-C), 115.6 (Ph-C), 114.8 (Ph-C), 110.4 (Ph-C), 55.5 (-OCH_3), 53.5 (-OCH_3), 52.3(-OCH_3); LC-MS: 99.9%; *m/z* (CI): 366.2 (M + H, 100%).

3-(1,2-Bis(4-fluorophenyl)-2a1,4,5-triazacyclopenta [cd]inden-3-yl)benzonitrile (30)

Bright yellow solid; Yield: 61%; mp: 275-279°C; IR (KBr) ν_{max}: 3061, 2854, 2227, 1514, 1234, 1143, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ 9.08 (d, $J = 5.2$ Hz, 1H, H-1), 7.93 (d, $J = 8.4$ Hz, 2H, H-17,15), 7.83 (d, $J = 5.6$ Hz, 1H, H-2), 7.49-7.31 (m, 6H, H-16,19,20,24,25,29), 7.17–7.08 (m, 4H, H-21,23,26,28); ^{13}C NMR (400 MHz, $CDCl_3$): δ 166.8 (Ph-C), 164.7 (Ph-C), 164.3 (Ph-C), 150.5 (Ph-C), 142.9 (Ph-C), 140.2 (Ph-C), 136.5 (Ph-C), 135.9 (Ph-C), 135.02 (Ph-C), 135.00 (Ph-C), 134.99 (Ph-C), 134.9 (Ph-C), 133.8 (Ph-C), 122.3 (Ph-C), 121.6 (Ph-C), 119.8 (Ph-C), 117.2 (Ph-C), 116.9 (Ph-C); LC-MS: 96%; *m/z* (CI): 433.3 (M + H, 100%).

3-(1,2-Diphenyl-2a1,4,5-triazacyclopenta[cd]inden-3-yl)benzonitrile (31)

Orange solid; Yield: 82%; mp: 253-256 °C; IR (KBr) ν_{max}: 3410, 3062, 2228, 1850, 1695, 965, 854 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ 9.1 (d, $J = 5.2$ Hz, 1H, H-1), 8.26 (d, $J = 8.0$ Hz, 1H, H-17), 8.0 (s, 1H, H-19), 7.94 (d, $J =$ 5.2 Hz, 1H, H-2), 7.64 (d, $J = 8.0$ Hz, 1H, H-15), 7.58–7.54 (m, 1H, H-16), 7.5–7.33 (m, 10H, H-20-29); ^{13}C NMR (400 MHz, $CDCl_3$): δ 153.3 (C-1), 148.8 (C-3), 147.1 (Ph-C), 135.9 (Ph-C), 135.6 (Ph-C), 134.0 (Ph-C), 133.6 (C-10), 133.4 (C-11), 133.4 (Ph-C), 132.8 (Ph-C), 132.4 (Ph-C), 130.2 (Ph-C), 129.7 (Ph-C), 129.6 (Ph-C), 129.4 (Ph-C), 129.1 (Ph-C), 128.9 (Ph-C), 128.3 (Ph-C), 127.7 (Ph-C), 123.2 (Ph-C), 117.9 (C-30), 112.8 (Ph-C), 108.8 (Ph-C); LC-MS: 99.5%; *m/z* (CI): 397.4 (M + H, 100%).

3-(1,2-Di(pyridin-2-yl)-2a1,4,5-triazacyclopenta[cd] inden-3-yl)benzonitrile (32)

Yellow solid; Yield: 65%; mp: 173-177 °C; IR (KBr) ν_{max}: 3433, 3062, 2228, 1584, 1066, 771, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1H, H-1), 8.96 (s, 1H, H-23), 8.7 (s, 1H, H-26), 8.47-8.39 (m, 2H, H-21,28), 8.03 (s, 1H, H-2), 7.87 (m, 1H, H-15), 7.68 (d, $J = 8.0$ Hz, 1H, H-17), 7.58–7.49 (m, 4H, H-27,29,20,22,), 7.23 (m, 1H, H-16), 7.13 (d, $J = 7.2$ Hz, 1H, H-19); ^{13}C NMR (400 MHz, $CDCl_3$): δ 154.3 (C-1), 152.7 (C-3), 152.3 (C-5), 150.7 (Ph-C), 150.2 (Ph-C), 148.7 (Ph-C), 137.2 (Ph-C), 136.3 (Ph-C), 135.7 (Ph-C), 134.4 (Ph-C), 134.0 (Ph-C), 133.6 (Ph-C), 133.4 (Ph-C), 129.4 (Ph-C), 128.3 (Ph-C), 125.9 (Ph-C), 124.4 (Ph-C), 123.4 (Ph-C), 123.2 (Ph-C), 122.2 (Ph-C), 118.1 (Ph-C), 112.6 (Ph-C), 112.0 (Ph-C), 29.59 (-OCH_3); LC-MS: 93%; *m/z* (CI): 399.1 (M + H, 100%).

4-(1,2-Di-p-tolyl-2a1,4,5-triazacyclopenta[cd]inden-3-yl)benzonitrile (33)

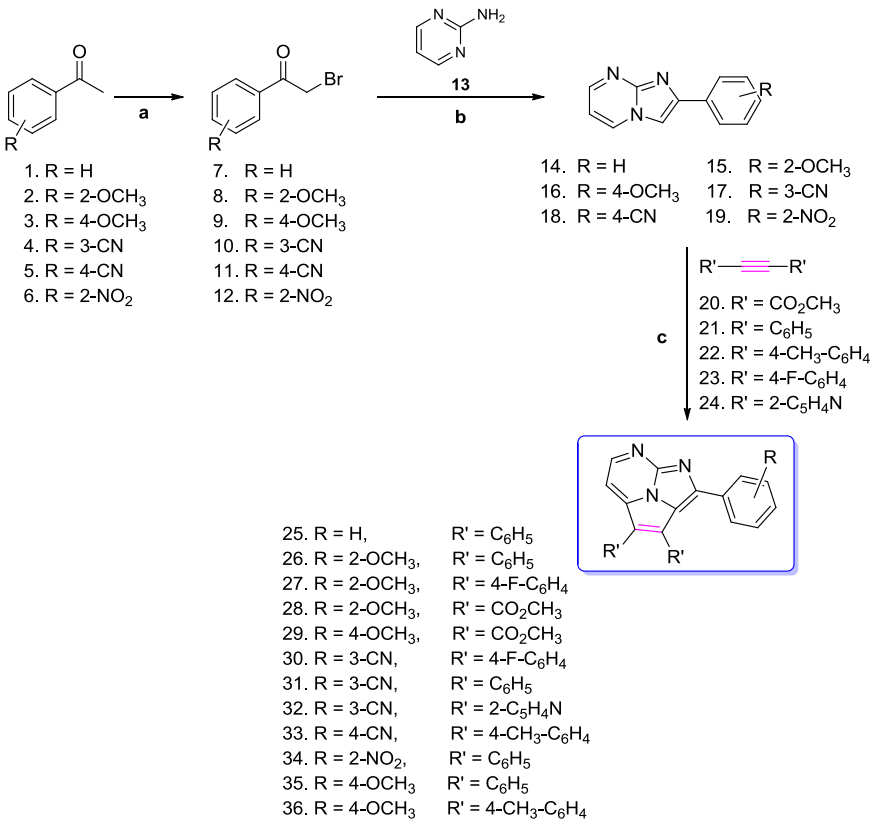
Yellow solid; Yield: 68%; mp: 256-258 °C; IR (KBr) ν_{max}: 3453, 2746, 2227, 1888, 1538, 815, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.11 (d, $J = 4.8$ Hz, 1H, H-1), 8.02 (d, $J = 8.4$ Hz, 2H, H-25,29), 7.91 (d, $J = 3.2$ Hz, 1H, H-2), 7.6 (d, $J = 8.0$ Hz, 2H, H-26,28), 7.32–7.22 (m, 8H, H-15,16,18,19,20,21,23,24), 2.47 (s, 3H, H-32), 2.39 (s, 3H, H-33); ^{13}C NMR (400 MHz, $CDCl_3$): δ 153.28 (C-1), 148.23 (C-3), 147.09 (C-5), 139.3 (Ph-C), 137.7 (Ph-C), 137.1 (Ph-C), 136.0 (Ph-C), 132.1 (Ph-C), 130.4 (Ph-C), 130.3 (Ph-C), 129.9 (Ph-C), 129.7 (Ph-C), 129.7 (Ph-C), 129.6 (Ph-C), 128.6 (Ph-C), 123.4 (Ph-C), 118.6 (Ph-C), 113.4 (Ph-C), 108.8 (Ph-C), 21.4 (CH_3), 21.2 (CH_3); LC-MS: 97%; *m/z* (CI): 425.4 (M+H, 100%).

3-(2-Nitrophenyl)-1,2-diphenyl-2a1,4,5-triazacyclopenta[cd]indene (34)

Pale green solid; Yield: 64%; mp: >400 °C; IR (KBr) ν_{max}: 3068, 2925, 2812, 1750, 1624, 986, 865, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.68 (q, $J = 2.1$ Hz, 1H, H-1), 7.79 (m, 2H, H-2,18), 7.55 (d, $J = 7.8$ Hz, 1H, H-17), 7.45 (dd, $J_1 = 1.8$ Hz, $J_2 = 6.9$ Hz, 1H, H-16), 7.41–7.32 (m, 3H, H-15,20,24), 7.3-7.23 (m, 5H, 21, 23, 25, 29, 26), 7.2-7.16 (m, 2H, H-22,28), 6.6 (q, $J =$ 3.9 Hz, 1H, H-27); ^{13}C NMR (400 MHz, $CDCl_3$): δ 161.8 (C-1), 150.0 (C-3), 147 (Ph-C), 141.3 (Ph-C), 136.7 (Ph-C), 134.4 (Ph-C), 133.4 (Ph-C), 133.2 (Ph-C), 130.4 (Ph-C), 129.2 (Ph-C), 128.9 (Ph-C), 128.6 (Ph-C), 128.3 (Ph-C), 127.2 (Ph-C), 124.1 (Ph-C), 123.4 (Ph-C), 118.82 (Ph-C), 116.4 (Ph-C), 113.7 (Ph-C); LC-MS: 95%; *m/z* (CI): 417.14 (M + H, 100%).

3-(4-methoxyphenyl)-1,2-diphenyl-2a1,4,5-triazacyclopenta[cd]indene (35)

Bright yellow solid; Yield: 74%; mp: 249-251 °C; IR (KBr) ν_{max}: IR: 3439, 2922, 2562, 1732, 1604, 1256, 1027, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H, H-1), 7.9 (d, $J = 6.0$ Hz, 2H, H-25,29), 7.83 (d, $J = 2.8$ Hz, 1H, H-2), 7.49–7.29 (m, 10H, H-15-24), 6.8 (d, $J = 12$ Hz, 2H, H-26,28), 3.8 (s, 3H, H-31); ^{13}C NMR: (400 MHz, $CDCl_3$) δ 161.8 (C-1), 147.8 (C-3), 146.8 (C-5), 135.6 (Ph-C), 134.4 (Ph-C), 133.5 (Ph-C), 133.0 (Ph-C), 131.7 (Ph-C), 130.6 (Ph-C), 129.7 (Ph-C), 128.8 (Ph-C), 128.7 (Ph-C), 127.3 (Ph-C), 127.0 (Ph-C), 125.4 (Ph-C), 113.9 (Ph-C), 107.8 (Ph-C), 55.7 (-OCH_3); LCMS: 99.9%; *m/z* (CI) 402.4 (M + H, 100%).



Scheme 1 Synthesis of 1,2-3-substituted-2a1,4,5-triazacyclopenta[cd]indene **25**–**36** Reaction conditions: **a** CuBr, 2-Me-THF, room temperature, 24 h; **b** $NaHCO_3$, 2-Me-THF, 2-aminopyrimidine, 85 °C, 10 h; **c** $Pd(OAc)_2$, $Cu(OAc)_2$, TBAB, DMF, 90 °C, 12 h

3-(4-methoxyphenyl)-1,2-di-p-tolyl-2a1,4,5-triazacyclopenta[cd]indene (36)

Bright yellow solid; Yield: 65%; mp: 186-189 °C; IR (KBr) ν_{max}: 3510, 3018, 1675, 1173, 879, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ 8.96 (d, $J = 5.6$ Hz, 1H, H-1), 7.93 (d, $J = 8.8$, 2H, H-25,29), 7.8 (d, $J = 5.6$, 1H, H-2), 7.35–7.21 (m, 8H, H-15,16,18,19,20,21,23,24), 6.83 (d, $J = 8.8$ Hz, 2H, H-26,28), 3.85 (s, 3H, H-33), 2.45 (s, 3H, H-32), 2.38 (s, 3H, H-31); ^{13}C NMR (400 MHz, $CDCl_3$): δ 161.7 (Ph-C), 157.0 (Ph-C), 147.7 (Ph-C), 146.7 (Ph-C), 138.6 (Ph-C), 137.1 (Ph-C), 135.6 (Ph-C), 134.6 (Ph-C), 131.7 (Ph-C), 130.5 (Ph-C), 130.4 (Ph-C), 130.2 (Ph-C), 129.5 (Ph-C), 129.4 (Ph-C), 126.9 (Ph-C), 125.6 (Ph-C), 122.5 (Ph-C), 113.9 (Ph-C), 107.6 (Ph-C), 55.4 (-OCH_3), 21.5 (-CH_3), 21.2 (-CH_3); LCMS: 99%; *m/z* (CI) 430.4 (M + H, 100%).

Experimental section for the evaluation of anti-inflammatory activity

Carrageenan induced paw edema test method (Winter et al. 1962; Kumar Reddy, Niren 2017; Kumar Reddy, Niren 2016) (Wistar rats) was adopted for the evaluation of anti-inflammatory activity for the synthesized 1,2-3-substituted-2a1,4,5-triazacyclopenta[cd]indenes **25**–**36**. Paw edema was induced by injecting 0.1 mL of 1% w/v carrageenan suspended in 1% CMC into sub-plantar tissues of the left hind paw of each rat. The paw thickness was measured before injecting the carrageenan and after 60, 120, 180 min using Vernier callipers. The anti-inflammatory activity was calculated as percentage inhibition of edema in the animals treated with compounds **25**–**36** in comparison to the carrageenan control group. The study was carried out as per the protocols approved by the Institutional Animal Ethical Committee (IAEC) of CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals). The animals were starved overnight and administered with Diclofenac sodium (standard drug) at dose of 10 mg/kg and test compounds (**25**–**36**, 10 mg/kg i.p), were controlled orally using gastric canula, 30 min before the carrageenan injection in sub-plantar region of left hind paw.

The percentage (%) inhibition of edema was calculated using the formula

$$\%\,\text{inhibition} = T_o - T_t/T_o \times 100$$

Where T_t is the thickness of paw of rats administered test extract at corresponding time and T_o is the paw thickness of rats of control group at the same time. The results of 0 h

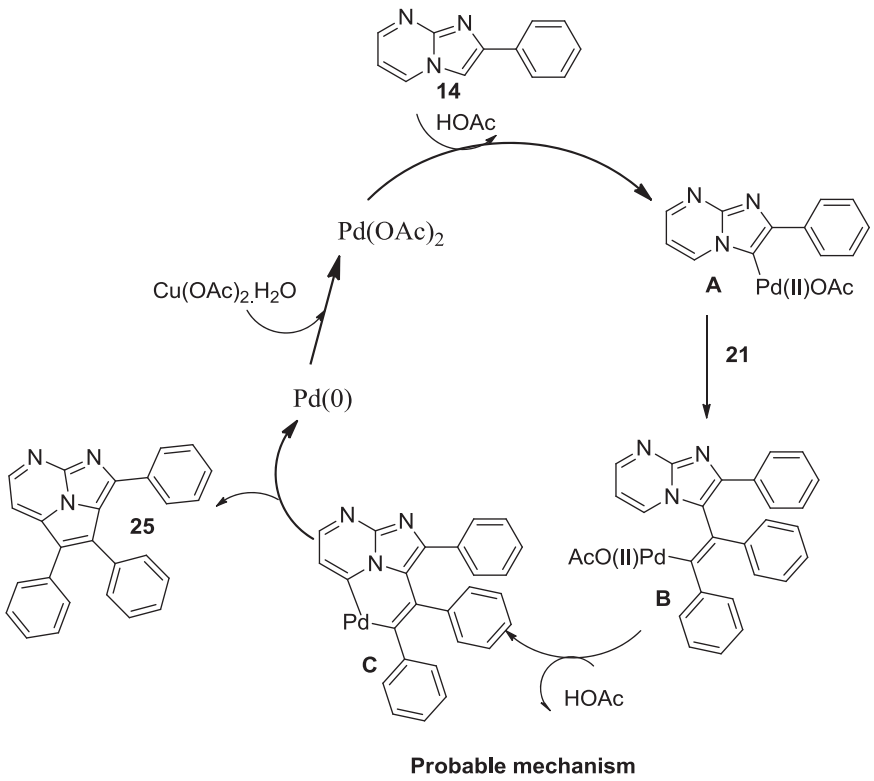


Fig. 1 Plausible reaction mechanism

control sample and Diclofenac standard drug administration and 3 h after dosage administration are illustrated in Fig. 3 and Fig. 4, respectively.

Results and discussion

Chemistry

The synthesis of 1,2,3-substituted-2a1,4,5-triazacyclopenta [cd]indene **25–36** is illustrated in (Scheme 1). Bromination of acetophenones **1–6** in presence of copper(II)bromide in 2-Me-tetrahydrofuran at room temperature for 12 h produced the corresponding acyl bromides (Raghunath et al., 2015) **7–12**. For Bromination, $CuBr_2$ was found to be a versatile reagent, as well as a clean process when compared to the usage of the liquid bromine for the preparation of acylbromides. Condensation of 2-bromo-1-(substituted phenyl)ethanones **7–12** with 2-aminopyrimidine in presence of sodium bicarbonate in 2-Me-tetrahydrofuran in sealed tube at 85 °C for 10 h resulted in the formation of various corresponding imidazo[1,2-a]pyrimidines **14–19**. These compounds when treated with 1,2-diaryl/diaklylethynes **20–24** in presence of $Pd(OAc)_2$, $Cu(OAc)_2$ and TBAB in DMF:PEG-1500 in sealed tube at 90 °C for 12 h resulted in the formation of the 1,2-3-substituted 2a1,4,5-triazacyclopenta[cd]indene derivatives **25–36** in good to excellent yields. It is worth mentioning that the above reaction conditions led to the exclusive formation of 1,2-3-substituted 2a1,4,5-triazacyclopenta[cd]indene derivatives **25–36** exclusively rather than the formation of the fused tetra cyclic ring system (Sanjay et al. 2016). The acetylenes **20** and **21** are commercially available, while the remaining acetylenes **22–24** were prepared according to the reported literature procedures. (Norio et al. 2010; Manashi et al. 2016; Ulrik, Pombo-Villar 2005).

The investigation into the plausible reaction mechanism for the exclusive formation of these derivatives is based on the previous literature a plausible reaction mechanism for these dehydrogenative annulations is outlined above. Possibly the initial formation of the active intermediate A is formed through electrophilic palladation at the 3-position of imidazopyrimidine moiety and the resulting intermediate A inserts into biphenylalkyne to produce a vinylicpalladium (II) intermediate B. Subsequently this intermediate **B** produces six-membered palladacycle C through C–H activation. Finally the Intermediate C afforded the corresponding 2,3,4-triarylphenyl-1,7b-triaza-cyclopenta[cd]indene derivative via reductive elimination along with the generation of Pd(0). This Pd(0) is reoxidized to the Pd(II) species by Cu $(OAc)_2.H_2O$ to complete the catalytic cycle as represented in Fig. 1.

The structural elucidation of these derivatives has been performed by ^{1}H NMR, ^{13}C NMR, LC-MS, and IR spectroscopy. As a representative sample, 3-(1,2-Diphenyl-2a1,4,5-triazacyclopenta[cd]inden-3-yl)benzonitrile (**31**)

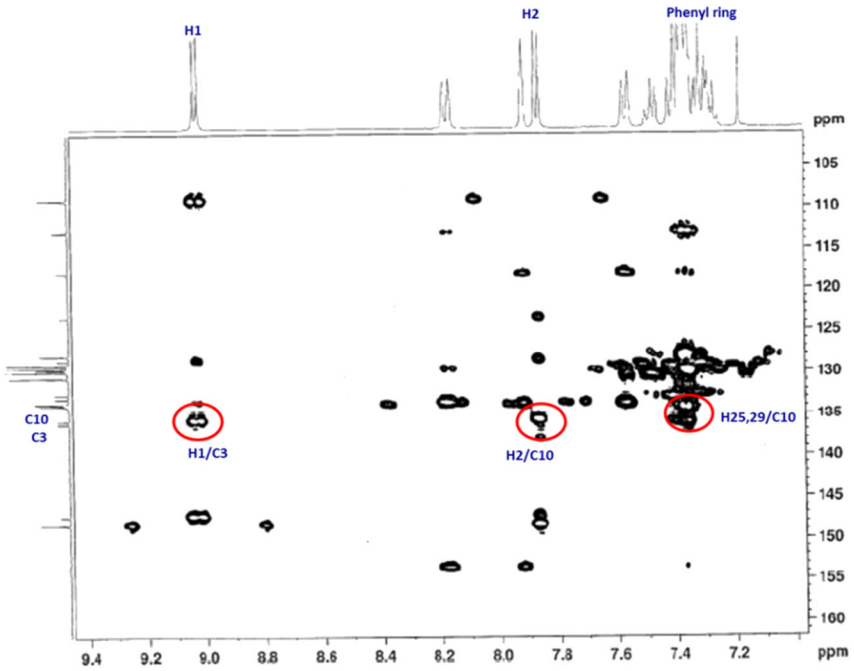


Fig. 2 ^{1}H–^{13}C gHMBC spectrum, key correlations shown with red colored circles and also key proton and carbons numbering given (color figure online)

was completely characterized. We have performed proton and carbon NMR to know number of proton and carbon atoms, and also for chemical shifts, respectively. Distortionless Enhancement by Polarization Transfer (DEPT-135^{0}) to find out number of protonated carbons and its type, gradient proton–proton correlation spectroscopy (gCOSY) (Fig. 2) to know the information about adjacent coupled partners (protons), gradient hetero nuclear single quantum coherence spectroscopy (gHSQC) to know about ^{1}J correlation between proton and carbon (which proton is attached to which carbon), gradient hetero nuclear multiple bond correlation spectroscopy (gHMBC) (Fig. 1) to know the ^{3}J correlations between proton and carbons. Other than ^{3}J couplings, ^{2}J and ^{4}J were also observed in gHMBC data (Fig. 1). The N15 HMBC experimental data revealed the chemical shifts of pyrimidine ring nitrogen.

There are 16 protons detected in aromatic region of proton NMR as based on integration, out of which two of the protons signals resonating at 9.10 ppm and 7.94 ppm as doublets with coupling constant (J) of 4.0 Hz are assigned to pyrimidine ring protons. The splitting pattern of four proton signals resonating at 8.20 ppm (doublet of triplet), 8.00 ppm (weak triplet), 7.66 ppm (doublet of triplet), and 7.46 ppm (strong triplet) confirms the presence of 1, 3-disubstituted benzene ring (3-cyano phenyl ring), which is merged in phenyl ring protons and its presence is confirmed by gCOSY (Fig. 3) experimental data. Presence of cyano group is confirmed by the correlation between H17 and H19 to C30 in gHMBC (Fig. 2) data and its carbon value is at 117.9 ppm. Ortho protons of one of the phenyl ring (H25 and H29) and H2 were showing 3J correlation with C10 at 135.60 ppm in gHMBC data (Fig. 2). The presence of only two protons on pyrimidine ring and C10 correlation with phenyl ring protons and H2 confirms that the cyclisation has happened on pyrimidine ring. Thus the above spectroscopic description confirms the structure of compound **31**. Similarly, the remaining compounds in the series are in agreement with the desired structure.

Anti-inflammatory activity

Table 1 illustrates the results of the anti-inflammatory activity of the above synthesized compounds **25**-**36**. Compounds **28** (R = 2-methoxy, R' = Phenyl), **30** (R = 3-CN, R' = 4-F-Phenyl), **33** (R = 4-CN, R' = 4-CH_3-Phenyl) and **35** (R = 4-methoxy, R' = Phenyl) exhibited good anti-inflammatory activity with 68%, 68.8%, 68%, and 68.4% inhibition, respectively (w.r.t. Diclofenac sodium, 71.1% inhibition). Figure 4 shows the control group rat paw, Diclofenac administered rat paw, and compound 30 and 35 administered rat paw images at 0 h. Figure 5 shows the control group rat paw, Diclofenac administered rat paw, and compound **30** and **35** administered rat paw images after 3 h. Compounds **26** (R = 2-methoxy, R' = Phenyl), **31** (R = 3-CN, R' = Phenyl) and **34** (R = 2-NO_2, R' = Phenyl), showed moderate anti-inflammatory activity with 66.6%, 66.6%, 67.1% inhibition while compounds **25** (R = H, R' = Phenyl), **27** (R = 2-methoxy, R' = 4-F-Phenyl), **29** (R = 4-methoxy, R' = CO_2CH_3), **32** (R = 3-CN, R' = 3-Pyridyl) and **36** (R = 4-methoxy, R' = 4-CH_3-Phenyl) displayed weak anti-inflammatory activity with 63.5%, 64.4%, 62.2%, 63.4%, 65.3% inhibition.

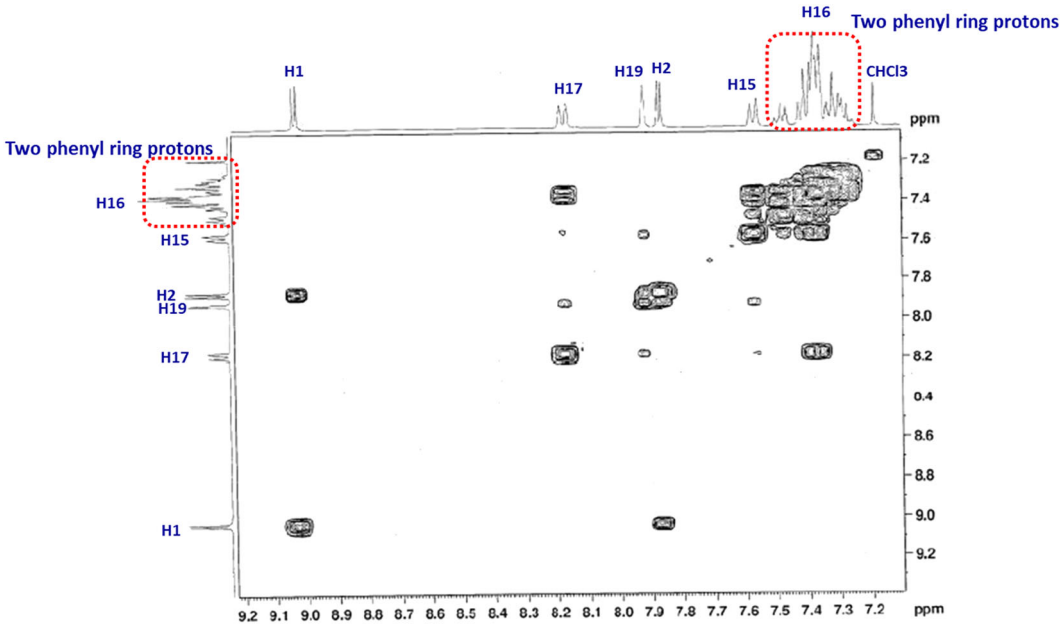


Fig. 3 ^{1}H–^{1}H COSY spectrum of compound **31**, H1, H2 proton correlation belongs to pyrimidine ring; H17, H19, H15, and H16 correlations belongs to 3-cyano phenyl ring; red colored dotted box indicates the correlation of two phenyl rings which are overlapped together (color figure online)

Table 1 Anti-inflammatory activity of 1,2-3-substituted-2a1,4,5-triazacyclopenta[cd] indenes **25–36**

Treatments	60 min	120 min	180 min	Percentage of inhibition at 180 min
Carrageenan control	1.4 ± 0.04	1.85 ± 0.064	2.25 ± 0.06	–
25	**1.110 ± 0.02*****	**1.255 ± 0.044*****	**0.82 ± 0.03*****	**63.5**
26	**1.18 ± 0.03*****	**1.115 ± 0.020*****	**0.72 ± 0.028*****	**66.6**
27	**1.15 ± 0.08*****	**1.22 ± 0.06*****	**0.80 ± 0.04*****	**64.4**
28	1.22 ± 0.04***	1.18 ± 0.035***	0.72 ± 0.025***	68.0
29	**1.175 ± 0.06*****	**1.375 ± 0.02*****	**0.85 ± 0.02*****	**62.2**
30	1.025 ± 0.058***	0.82 ± 0.056***	0.70 ± 0.004***	68.8
31	**1.2 ± 0.04*****	**1.225 ± 0.025*****	**0.75 ± 0.02*****	**66.6**
32	**1.175 ± 0.04*****	**1.2 ± 0.04*****	**0.822 ± 0.25*****	**63.4**
33	1.045 ± 0.062***	0.87 ± 0.067***	0.72 ± 0.003***	68.0
34	**0.90 ± 0.08*****	**0.81 ± 0.02*****	**0.74 ± 0.06*****	**67.1**
35	**1.1 ± 0.08*****	**0.97 ± 0.047*****	**0.71 ± 0.002*****	**68.4**
36	**1.075 ± 0.06*****	**0.8 ± 0.04*****	**0.78 ± 0.002*****	**65.3**
Diclofenac sodium (10 mg/kg)	0.92 ± 0.025***	0.8 ± 0.04***	0.65 ± 0.02***	71.1

Note: Values are expressed as mean ± S.E.M of 4 animals. Superscript letters represent the statistical significance done by ANOVA, followed by Tukey's multiple comparison tests. $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ indicates comparison of with control group with negative control and negative control with treatment groups

Conclusion

In conclusion, the present study describes the synthesis of some novel 1,2-3-substituted-2a1,4,5-triazacyclopenta[cd] indene derivatives **25–36**. These derivatives were characterized by ^{1}H NMR, Mass, and IR spectral data and were further evaluated for anti-inflammatory activity using Carrageenan induced paw edema test method in which they showed comparable anti-inflammatory activity against the drug Diclofenac sodium. Compounds **28** (R = 2-methoxy, R' = Phenyl), **30** (R = 3-CN, R' = 4-F-Phenyl), **33** (R = 4-CN, R' = 4-CH_3-Phenyl), and **35** (R = 4-methoxy, R' = Phenyl) exhibited good anti-inflammatory activity with 68%, 68.8%, 68%, and 68.4% inhibition, respectively

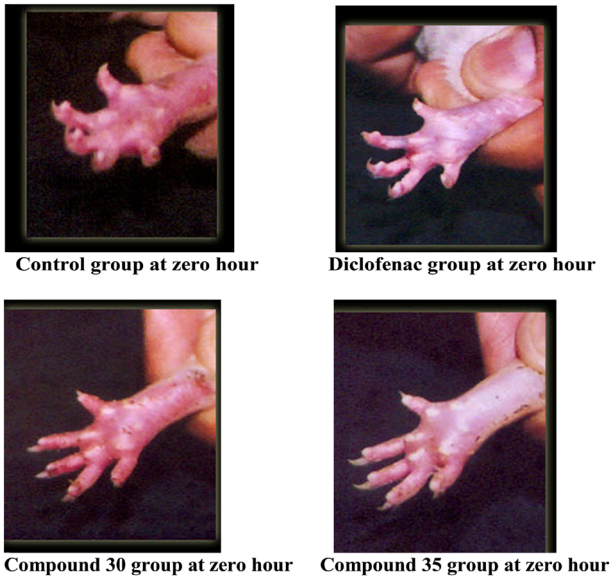


Fig. 4 The rat paw edema snap was taken at the time of carrageenan administration at the 0 h, Compound **30**, Compound **35**

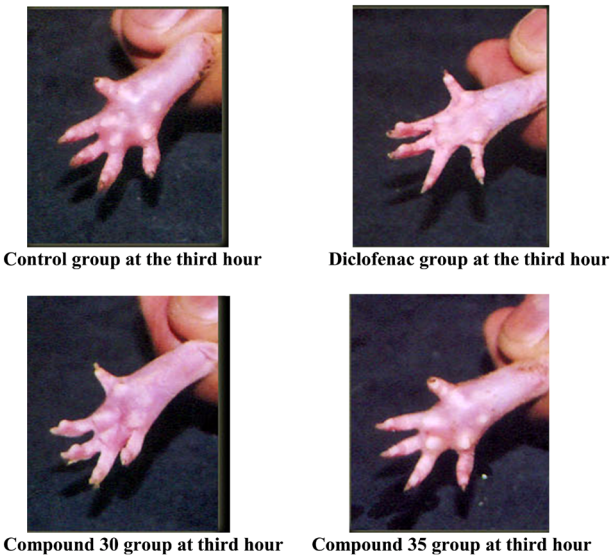


Fig. 5 The rat paw edema snap was taken at the third hour of carrageenan administration and after the administration of Diclofenac, Compound **30**, Compound **35**

(w.r.t. Diclofenac sodium, 71.1% inhibition) and the remaining compounds in the series displayed moderate to weak anti-inflammatory activity. Thus, these comparable results specify further generation of similar libraries with different substituents to discover potential anti-inflammatory compounds which can serve as newer lead candidates.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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