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Super acid catalysed sequential hydrolysis/cycloisomerization of *o*-(acetylenic)benzamides under microwave condition: Synthesis, antinociceptive and antiinflammatory activity of substituted isocoumarins

CHANDRASEKARAN PRAVEEN[a], P DHEENKUMAR[b] and P T PERUMAL[a,*]

[a]Organic Chemistry Division, Central Leather Research Institute (CSIR), Adyar, Chennai 600 020, India
[b]Department of Pharmaceutical Chemistry, EGS Pillay College of Pharmacy, Nagapattinam 611 002, India
e-mail: ptperumal@gmail.com

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Abstract. Synthesis of isocoumarins and related compounds via triflic acid promoted hydrolysis/cyclization sequence of 2-(alkynyl)benzamides under microwave condition was achieved. The substrate scope of the reaction was broad to include not only aromatic but also polyaromatic and heteroaromatic motifs, thus highlighting the significance of this methodology. One-pot operation, short reaction time, good chemical yields and excellent regioselectivity are the advantages of this protocol. All the synthesized compounds were evaluated for their antinociceptive and antiinflammatory activities using *in vivo* rodent models.

Keywords. Microwave; sequential process; isocoumarins; antinociceptive; antiinflammatory.

1. Introduction

Trifluoromethane sulphonic acid (CF_3SO_3H or HOTf), also known as triflic acid, is the strongest Brønsted acid (pKa -13.6) available at industrial scale.[1] It is one of the small group of acids commonly known as 'super acids', being stronger than concentrated H_2SO_4. Amongst this special class of compounds, triflic acid has several important advantages. It is non-oxidizing, has a high thermal stability, is resistant to both oxidation and reduction and does not yield fluoride ions, even in the presence of strong nucleophiles.[2] Unlike H_2SO_4, FSO_3H or $ClSO_3H$, it does not lead to sulphonations and can be used in various protonation reactions.[3] This novel collection of properties has made triflic acid an important reagent and catalyst in modern synthetic chemistry. As a comparatively new substance, it was first reported in 1954[4] and subsequently commercialized,[5] researchers continue to find new and interesting applications of triflic acid.[6]

On the other hand, development of effective strategies for the synthesis of a large structural diversity of heterocyclic compounds is a very important challenge in modern organic synthesis.[7] In particular, the synthesis of low molecular weight heterocyclic compounds with potential pharmacological properties has attracted considerable attention due to the need in identifying active compounds by high-throughput screening of large combinatorial libraries.[8] Recently, a seminal study was carried out by Uchiyama *et al*. using HOTf as catalyst in the regioselective cyclization of 2-(alkynyl)benzoic acids leading to isocoumarins.[9] Moreover, Bianchi *et al*. reported the direct synthesis of 3-substituted isocoumarins through silver catalysed heteroannulation of *o*-(1-alkynyl)benzamides.[10] However, these methodologies are applicable for few substrates and a great deal of interest exists in the synthesis of isocoumarin library.[11] In connection with our ongoing interest in developing new synthetic strategies for the construction of heterocycles[12] under HOTf acid catalysis,[12c] we were interested in the sequential hydrolysis/cycloisomerization of 2-(alkynyl)benzamides[13] leading to isocoumarins,[14] with particular emphasis on performing this transformation under microwave condition.[15]

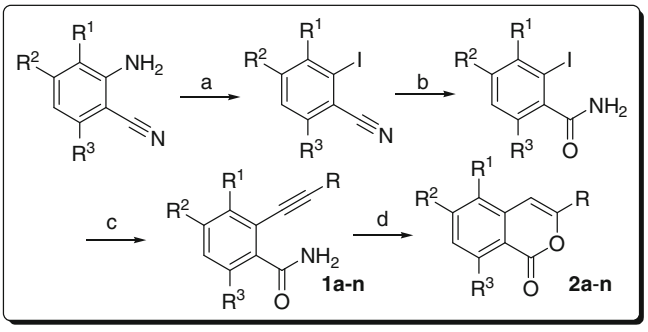
2. Experimental

2.1 *Materials, methods and instruments*

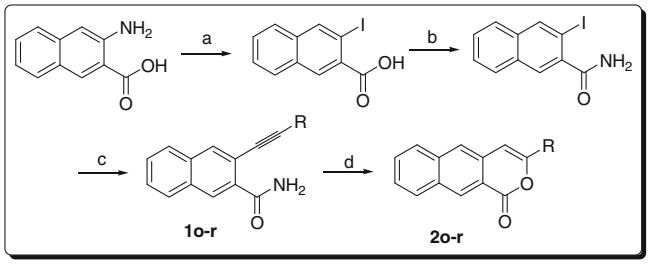
All commercially available solvents and reagents were used without further purification. Anhydrous solvents were purchased from Sigma-Aldrich. All reactions of

*For correspondence

air and water sensitive materials were performed in flame dried glassware under a positive atmosphere of nitrogen or argon using standard syringe, cannula and septa techniques. Solutions in organic solvents were dried with anhydrous sodium sulphate. Solvents were evaporated under reduced pressure. Melting points were obtained using a Kofler–Galen hot stage microscope and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR spectrophotometer as KBr pellets for solid compounds and neat sample for liquid compounds. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ and DMSO-d_6 on a JEOL spectrometer at 500 and 125 MHz, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and expressed in parts per million. The number of protons (n) for a given resonance was indicated as nH. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet) and m (multiplet). Coupling constants (J) are given in hertz. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage MAX 6000 ESI mass spectrometer using electrospray ionization method. GC-MS were recorded using a Perkin–Elmer Auto System XL Gas Chromatograph with a Turbo-Mass Mass Spectrometer (EI, 70 ev), with helium as carrier gas at a flow rate of 1 mL/min, Perkin–Elmer Elite series PE-5, capillary column (30 m × 0.25 mm × 1 μm), oven programmed between 100 and 260°C at the rate of 10°C/min. Elemental analyses were recorded using a Thermo Finnigan FLASH EA 1112CHN analyzer. All the compounds gave C, H and N analysis within ±0.5% of the theoretical values. All microwave experiments were performed using a BPL microwave cooking system model BMO-700T, manufactured by BPL-SANYO Utilities and Appliances Ltd, Bangalore,

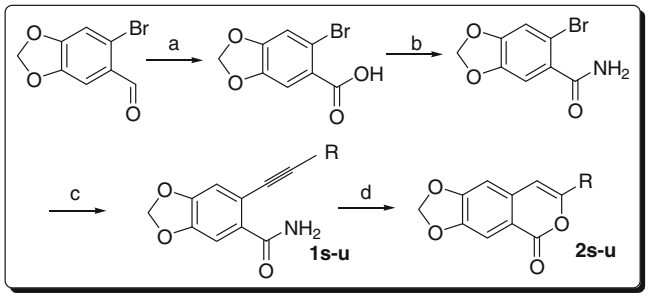


Scheme 1. Reagents and condition: (a) 1.1 equiv. $NaNO_2$/25% HCl, 0 to 5°C, 30 min, then 1.2 equiv. KI (aqueous), 5°C to rt, 4 h; (b) 30% H_2O_2/3.0 equiv. Na_2CO_3, Acetone, 5°C to rt, 1 h; (c) 5 mol% $Pd(PPh_3P)_2Cl_2$/5 mol% CuI/Et_3N, rt, 15 min, N_2 then 1.1 equiv. terminal alkyne; (d) 1.0 equiv. TfOH, toluene, 300 W, 3 min.



Scheme 2. Reagents and condition: (a) 1.1 equiv. $NaNO_2$/25% HCl, 0 to 5°C, 30 min, then 1.2 equiv. KI (aqueous), 5°C to rt, 4 h; (b) 3.0 equiv. PCl_5, Et_2O, 0 to 5°C, 1 h then excess NH_3 (aq.), 0°C to rt, 2 h; (c) 5 mol% $Pd(PPh_3P)_2Cl_2$/5 mol% CuI/Et_3N, rt, 15 min, N_2 then 1.1 equiv. terminal alkyne; (d) 1.0 equiv. TfOH, toluene, 300 W, 3 min.

India. The oven has variable timing cycles from 1 s to 99 min and 99 s and heating cycles from 155 to 700 W of power output which can be varied by selecting power levels ranging from 10 to 100. The overall dimension of the domestic oven is 525 (W) × 419 (D) × 281 (H) mm with a chamber of 350 (W) × 370 (D) × 208 (H) mm. The microwave frequency is 50 Hz and the oven capacity is 26 litres. Column chromatography was performed using a mixture of petroleum ether and ethyl acetate on silica gel (100–200 mesh, SRL, India). Analytical TLC was performed on pre-coated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany) using analytical grade solvents and visualizing with iodine spray (10% w/w I_2 in silica gel) or UV light ($\lambda = 254$ and 365 nm). The inflammation was quantitated using a digital plethysmometer (Ugo Basile Company, Italy). The following reactions (schemes 1 to 3) were performed by published procedures: Sandmeyer iodination[16] of 2-aminobenzonitriles and 3-aminonaphthalene-2-carboxylic acid, Alkaline hydrolysis of 2-iodobenzonitriles,[17] Sonogashira cross-coupling of 2-halobenzamides,[18] conversion of acid to



Scheme 3. Reagents and condition: (a) 1.0 equiv. oxone, DMF, rt, 1 h; (b) 3.0 equiv. $SOCl_2$, Et_2O, 0 to 5°C, 1 h then excess NH_3 (aq.), 0°C to rt, 2 h; (c) 5 mol% $Pd(PPh_3P)_2Cl_2$/5 mol% CuI/Et_3N, rt, 15 min, N_2 then 1.1 equiv. terminal alkyne; (d) 1.0 equiv. TfOH, toluene, 300 W, 3 min.

amide,[19] oxone promoted oxidation of 6-bromo-piperanal,[20] conversion of indole-2-carboxylic acid to indole-2-carbonitrile,[21] C3-iodination of indole,[22] and N-alkylation of indole derivatives.[23]

2.2 *General procedure for the synthesis of isocoumarin derivatives **2a–2x***

Triflic acid (1.0 mmoL) was added to a mixture of 2-(alkynyl)benzamide (1.0 mmoL) and toluene (1 mL) in a glass vial and inserted in an alumina bath (100 g, 60 G_{254}, Fischer scientific bath (6.8 cm diameter)) and irradiated in a BPL-SANYO domestic microwave oven operating at 300 W at a pulse rate of 30 sec for 3 min. After cooling to room temperature, the reaction mixture was quenched with 10% $NaHCO_3$ solution, extracted with CH_2Cl_2 (3 × 15 mL) and the organic extract was dried with anhydrous $MgSO_4$. Removal of the solvent under reduced pressure followed by purification with column chromatography afforded the pure product.

2.2a *3-Phenyl-1H-isochromen-1-one (**2a**)*: Brown solid; mp 85–87°C (lit.[24] mp 87–88°C); IR (KBr): 1738, 1665 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 6.95 (s, 1H), 7.40–7.51 (m, 5H), 7.72 (t, 1H, J = 7.3 Hz), 7.88 (dt, 2H, J_1 = 1.5, J_2 = 8.1 Hz), 8.31 (d, 1H, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 101.8, 120.5, 125.2, 126.0, 128.1, 128.8, 129.7, 130.0, 132.0, 134.8, 137.5, 153.6, 162.3. MS (EI): m/z = 222 [M^+]. Anal. Calcd for $C_{15}H_{10}O_2$: C, 81.07; H, 4.54%. Found: C, 80.95; H, 4.52%.

2.2b *3-(3-Fluorophenyl)-1H-isochromen-1-one (**2b**)*: Colourless solid; mp 136–138°C (lit.[25] mp 138–140°C); IR (KBr): 1715 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 6.94 (s, 1H), 7.13 (td, 1H, J_1 = 8.0, J_2 = 2.5 Hz), 7.41–7.44 (m, 1H), 7.50–7.59 (m, 3H), 7.62–7.77 (m, 2H), 8.35 (d, 1H, J = 8.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 102.5, 112.1 ($J_{C\text{-}F}$ = 24.0 Hz), 117.0 ($J_{C\text{-}F}$ = 22.0 Hz), 120.6, 120.8 ($J_{C\text{-}F}$ = 3.0 Hz), 126.0, 128.5, 129.6, 130.5 ($J_{C\text{-}F}$ = 9.0 Hz), 134.0 ($J_{C\text{-}F}$ = 8 Hz), 135.0, 137.1, 152.2, 161.9, 163.1 ($J_{C\text{-}F}$ = 245.0 Hz). MS (EI): m/z = 240 [M^+]. Anal. Calcd for $C_{15}H_9O_2F$: C, 75.00; H, 3.78%. Found: C, 74.89; H, 3.82%.

2.2c *3-(4-Methoxyphenyl)-1H-isochromen-1-one (**2c**)*: Colourless solid; mp 143–145°C (lit.[26] mp 142–143°C); IR (KBr): 1727, 1566, 1478 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 3.87 (s, 3H); 6.80 (s, 1H); 6.97 (dt, 2H, J_1 = 9.2, J_2 = 2.8 Hz); 7.42–7.46 (m, 2H); 7.70 (td, 1H, J_1 = 7.1, J_2 = 1.3 Hz); 7.83 (dd, 2H, J_1 = 9.2, J_2 = 2.1 Hz); 8.30 (d, 1H, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 55.5, 100.1, 114.1, 114.2, 120.0, 124.6, 125.7, 126.7, 126.8, 127.6, 129.5, 134.9, 138.0, 153.7, 161.0, 162.4 162.5. MS (EI): m/z = 252 [M^+]. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79%. Found: C, 76.02; H, 4.82%.

2.2d *3-Butyl-1H-isochromen-1-one (**2d**)*: Brown solid; mp 45–47°C (lit.[27] mp 49.5–50.5°C); IR (neat): 2958, 1731, 1657 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.94 (t, 3H, J = 7.6 Hz); 1.36–1.45 (m, 2H); 1.66–1.75 (m, 2H); 2.54 (t, 2H, J = 7.6 Hz); 6.25 (s, 1H); 7.36 (d, 1H, J = 7.6 Hz); 7.63–7.69 (m, 1H); 8.23–8.27 (m,1H); 7.42–7.46 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 13.6, 22.1, 29.0, 37.6, 102.8, 122.9, 127.4, 1219.6, 130.3, 134.6, 136.0, 137.8, 158.4. MS (EI): m/z = 202 [M^+]. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98%. Found: C, 77.35; H, 7.02%.

2.2e *3-Hexyl-1H-isochromen-1-one*[28] *(**2e**)*: Yellow oil; IR (neat): 2928, 1733, 1655, 1158 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.89 (t, 3H, J = 6.9 Hz); 1.25–1.40 (m, 6H); 1.66–1.76 (m, 2H); 2.49–2.53 (m, 2H); 6.25 (s, 1H); 7.35 (d, 1H, J = 7.8 Hz); 7.41–7.45 (m, 1H); 7.65–7.69 (m, 1H); 8.23–8.25 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 13.9, 23.0, 28.5, 29.6, 30.2, 38.7, 102.8, 127.6, 129.3, 134.5, 137.5, 158.3, 163.1. MS (EI): m/z = 230 [M^+]. Anal. Calcd for $C_{15}H_{18}O_2$: 78.23; H, 7.88%. Found: C, 78.30; H, 7.81%.

2.2f *5-Nitro-3-phenyl-1H-isochromen-1-one (**2f**)*: Yellow solid; mp 140–142°C (lit.[29] mp 142–143°C); IR (KBr): 1349, 1522, 1744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.51–7.55 (m, 3H), 7.65 (t, 1H, J = 7.6 Hz); 7.85 (d, 1H, J = 0.8 Hz); 7.95–8.00 (m, 2H), 8.55 (dd, 1H, J_1 = 8.2, J_2 = 1.2 Hz); 8.69 (ddd, 1H, J_1 = 8.2, J_2 = 1.2, J_3 = 0.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 102.4, 114.2, 122.4, 126.5, 127.5, 128.6, 129.2, 129.3, 131.1, 136.2, 144.6, 148.9, 152.8, 164.0. MS (EI): m/z = 267 [M^+]. Anal. Calcd for $C_{15}H_9NO_4$: C, 67.42; H, 3.39; N, 5.24%. Found: C, 67.30; H, 3.41; N, 5.28%.

2.2g *5-Nitro-3-p-tolyl-1H-isochromen-1-one (**2g**)*: Yellow solid: mp 159–161°C (lit.[29] mp 161–162°C); IR (KBr): 1325, 1521, 1622, 1741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 2.41 (s, 3H); 7.27 (d, 2H, J = 8.4 Hz), 7.55 (t, 1H, J = 8.4 Hz); 7.79 (s, 1H); 7.81 (d, 2H, J = 8.4 Hz); 8.49 (dd, 1H, J_1 = 8.2, J_2 = 1.3 Hz); 8.63 (dt, 1H, J_1 = 8.2, J_2 = 1.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.9, 102.0, 113.8, 122.5, 126.2, 127.3, 128.9, 129.1, 131.0, 136.0, 144.5, 148.7, 152.3, 164.1. MS (EI): m/z = 281 [M^+]. Anal. Calcd

for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N, 4.98%. Found: C, 68.20; H, 3.97; N, 5.02%.

2.2h *3-(4-Methoxyphenyl)-5-nitro-1H-isochromen-1-one (**2h**)*: Yellow solid: mp 238–240°C (lit.[29] mp 241–242°C); IR (KBr): 1350, 1517, 1625, 1732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 3.89 (s, 3H); 6.97 (d, 2H, J = 9.1 Hz), 7.55 (t, 1H, J = 8.4 Hz); 7.77 (s, 1H); 7.90 (d, 2H, J = 9.1 Hz); 8.48 (dd, 1H, J_1 = 8.4, J_2 = 1.3 Hz); 8.61 (dd, 1H, J_1 = 8.4, J_2 = 1.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 55.8, 102.2, 114.0, 122.3, 126.0, 127.1, 128.5, 129.5, 131.4, 136.7, 143.9, 149.9, 161.4, 164.6. MS (EI): m/z = 297 [M^+]. Anal. Calcd for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73; N, 4.71%. Found: C, 64.50; H, 3.75; N, 4.77%.

2.2i *6-Methoxy-3-phenyl-1H-isochromen-1-one (**2i**)*: Colourless solid; mp 135–137°C (lit.[30] 136.5–137.0°C); IR (KBr): 1732, 1607, 1519, 720 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 3.94 (s, 3H); 6.90 (d, 1H, J = 2.6 Hz); 6.92 (s, 1H); 7.05 (dd, 1H, J = 2.6, 8.6 Hz); 7.43–7.48 (m, 3H); 7.85 (dd, 2H, J = 1.3, 8.6 Hz); 8.25 (d, 1H, J = 8.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 56.5, 101.9, 108.9, 109.9, 118.0, 125.0, 125.7, 128.9, 129.3, 130.5, 131.6, 136.7, 141.2, 155.1, 159.9, 162.5. MS (EI): m/z = 252 [M^+]. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79%. Found: C, 75.99; H, 4.84%.

2.2j *6-Methoxy-3-(4-methoxyphenyl)-1H-isochromen-1-one (**2j**)*: Colourless solid; mp 144–146°C (lit.[31] mp 145–147°C); IR (KBr): 1737, 1605, 1514, cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 3.87 (s, 3H); 3.93 (s, 3H); 6.75 (s, 1H); 6.83 (d, 1H, J = 2.6 Hz); 6.90–7.00 (m, 2H); 7.02 (dd, 1H, J_1 = 8.6, J_2 = 2.6 Hz); 7.75–7.88 (m, 2H); 8.20 (d, 1H, J = 8.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 55.4, 55.5, 100.1, 107.4, 113.3, 114.1, 114.2, 116.0, 124.4, 126.7, 126.8, 131.7, 140.0, 154.1, 161.0, 162.1, 164.3. MS (EI): m/z = 282 [M^+]. Anal. calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00%. Found: C, 72.45; H, 4.97%.

2.2k *8-Methoxy-3-phenyl-1H-isochromen-1-one (**2k**)*: Yellow solid; mp 142–144°C (lit.[32] mp 143–145°C); IR (KBr): 1723, 1569, 1480 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 4.02 (s, 3H); 6.85 (s, 1H); 6.95 (d, 1H, J = 8.0 Hz); 7.05 (d, 1H, J = 8.1 Hz); 7.40–7.54 (m, 3H); 7.65 (t, 1H, J = 8.0 Hz); 7.82–7.95 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 56.4, 101.7, 109.1, 109.9, 118.1, 125.2, 125.3, 128.6, 128.7, 129.8, 131.6, 135.6, 140.5, 153.8, 159.0, 161.7. MS (EI): m/z = 252 [M^+]. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79%. Found: C, 76.30; H, 4.75%.

2.2l *3-Ethyl-6-methoxy-1H-isochromen-1-one (**2l**)*: Colourless solid; mp 90–92°C (lit.[33] mp 93–95°C); IR (KBr): 3085, 2992, 1728, 1647, 1605, 1155 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.33 (t, 3H, J = 7.6 Hz); 2.61 (q, 2H, J = 7.6 Hz); 3.95 (s, 3H); 6.25 (s, 1H); 6.79 (d, 1H, J = 2.6 Hz); 7.03 (dd, 1H, J_1 = 8.6, J_2 = 2.6 Hz); 8.22 (d, 1H, J = 8.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 11.5, 27.0, 55.9, 102.5, 107.5, 113.6, 116.4, 132.1, 140.2, 160.5, 163.2, 165.2. MS (EI): m/z = 204 [M^+]. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%. Found: C, 70.30; H, 5.98%.

2.2m *6-Methoxy-3-methyl-1H-isochromen-1-one (**2m**)*: Colourless solid; mp 85–87°C (lit.[34] mp 86–88°C); IR (KBr): 3075, 2998, 1725, 1650, 1614, 1144 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 2.32 (s, 3H), 3.95 (s, 3H), 6.24 (s, 1H), 6.76 (d, 1H,J = 2.6 Hz), 7.02 (1H, dd, J_1 = 8.6, J_2 = 2.6 Hz, 1H), 8.20 (d, 1H, J = 8.6 Hz, 1H); 13C NMR (125 MHz, $CDCl_3$): δ_C 20.1, 56.1, 104.1, 107.3, 113.4, 116.2, 132.1, 140.3, 155.5, 163.1, 165.0. MS (EI): m/z = 190 [M^+]. Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30%. Found: C, 69.60; H, 5.26%.

2.2n *8-Fluoro-3-ethyl-1H-isochromen-1-one33 (**2n**)*: Colourless oil; IR (neat): 3083, 2973, 1743, 1661, 1614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.30 (t, 3H, J = 7.6 Hz); 2.59 (qd, 2H, J_1 = 7.6, J_2 = 1.3 Hz); 6.25 (t, 1H, J = 1.3 Hz); 7.05–7.17 (m, 2H); 7.60–7.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 11.4, 27.1, 102.0 (d, J_{C-F} = 3.1 Hz), 109.5 (d, J_{C-F} = 7.1 Hz), 114.9 (d, J_{C-F} = 21.0 Hz), 121.5 (d, J_{C-F} = 4.1 Hz),136.7 (d, J_{C-F} = 10.0 Hz), 140.5, 158.9 (d, J_{C-F} = 5.6 Hz), 161.2, 163.1 (d, J_{C-F} = 266.1 Hz). MS (EI): m/z = 192 [M^+]. Anal. Calcd for $C_{11}H_9FO_2$: C, 68.74; H, 4.72%. Found: C, 68.90; H, 4.66%.

2.2o *3-Phenyl-1H-benzo[g]isochromen-1-one (**2o**)*: Brown solid; mp 182–183°C; (lit.[35] mp 180.5–181°C); IR (KBr): 1730, 1629 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.06 (s, 1H); 7.40–7.50 (m, 3H); 7.56 (t, 1H, J = 7.6 Hz); 7.67 (t, 1H, J = 7.6 Hz); 7.91–7.92 (m, 4H); 8.02 (d, 1H, J = 8.3 Hz); 8.93 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 101.9, 119.0, 124.3, 125.1, 126.7, 127.7, 128.8, 129.4, 129.8, 129.8, 132.0, 132.1, 132.2, 132.4, 136.6, 152.0, 162.6. MS (EI): m/z = 272 [M^+]. Anal. Calcd for $C_{19}H_{12}O_2$: C, 83.81; H, 4.44%. Found: C, 83.45; H, 4.57%.

2.2p *3-Butyl-1H-benzo[g]isochromen-1-one* (***2p***): Pale yellow solid; mp 103–105°C; IR (KBr): 1728, 1625 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.95 (t, 3H, J = 6.9 Hz); 1.32–1.34 (m, 2H); 1.59–1.61(m, 2H); 2.55 (t, 2H, J = 6.9 Hz); 6.58 (s, 1H); 7.33 (d, 1H, J = 7.6 Hz); 7.52–7.62 (m, 1H); 7.77–7.86 (m,1H); 7.97–8.06 (m, 1H); 8.12 (s, 1H); 8.49 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 13.8, 22.3, 29.1, 37.9, 102.0, 125.2, 125.3, 126.5, 127.4, 128.5, 129.0, 129.3, 131.5, 134.0, 134.9, 151.8, 162.2. MS (EI): m/z = 252 [M^+]. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39%. Found: C, 81.04; H, 6.35%.

2.2q *3-p-Tolyl-1H-benzo[g]isochromen-1-one* (***2q***): Yellow solid; mp 159–161°C; IR (KBr): 1729, 1626 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 2.37 (s, 3H); 7.01 (s, 1H); 7.09 (d, 2H, J = 8.4 Hz); 7.27 (d, 2H, J = 8.4 Hz); 7.34–7.45 (m, 4H); 7.97 (s, 1H); 8.89 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 22.9, 100.2, 119.0, 124.9, 125.0, 126.1, 126.3, 126.5, 127.0, 127.2, 128.1, 129.0, 129.1, 131.3, 134.0, 134.9, 151.7, 162.7. MS (EI): m/z = 286 [M^+]. Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93%. Found: C, 84.05; H, 4.89%.

2.2r *3-o-Tolyl-1H-benzo[g]isochromen-1-one* (***2r***): Yellow solid; mp 166–168°C; IR (KBr): 1728, 1625 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 2.35 (s, 3H); 7.05 (s, 1H); 7.26–7.40 (m, 4H); 7.53–7.72 (m, 4H); 8.10 (s, 1H); 8.74 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 22.7, 100.3, 119.1, 121.0, 122.4, 124.7, 125.1, 126.2, 126.1, 126.7, 127.0, 127.3, 128.2, 129.0, 129.7, 131.5, 134.2, 134.9, 151.6, 162.5. MS (EI): m/z = 286 [M^+]. Anal. Calcd for $C_{19}H_{12}O_2$: C, 83.90; H, 4.93%. Found: C, 83.65; H, 4.99%.

2.2s *7-Phenyl-5H-[1,3]dioxolo[4,5-g]isochromen-5-one* (***2s***): Pale yellow solid; mp 113–115°C; IR (KBr): 1738, 1630, 1034, 755 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 5.91 (s, 2H); 6.71 (s, 1H); 7.04 (s, 1H); 7.15–7.24 (m, 3H); 7.29 (s, 1H); 7.33–7.39 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 98.5, 101.4, 111.1, 113.2, 122.4, 125.9, 128.1, 128.9, 131.2, 131.9, 145.1, 148.1, 154.0, 163.2. MS (EI): m/z = 266 [M^+]. Anal. Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79%. Found: C, 72.02; H, 3.84%.

2.2t *7-Butyl-5H-[1,3]dioxolo[4,5-g]isochromen-5-one* (***2t***): Colourless solid; mp 97–99°C; IR (KBr): 1733, 1627, 1035, 757 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 0.96 (t, 3H, J = 6.9 Hz); 1.33–1.36 (m, 2H); 1.54–1.62 (m, 2H); 2.10 (t, 2H, J = 6.9 Hz); 5.90 (s, 2H); 6.13 (s, 1H); 6.98 (s, 1H); 7.51 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 13.9, 22.8, 29.1, 36.9, 101.9, 102.3, 117.1, 121.0, 122.9, 132.2, 148.2, 151.1, 154.6, 162.0. MS (EI): m/z = 246 [M^+]. Anal. Calcd for $C_{19}H_{12}O_2$: C, 68.28; H, 5.73%. Found: C, 68.45; H, 5.69%.

2.2u *7-p-Tolyl-5H-[1,3]dioxolo[4,5-g]isochromen-5-one* (***2u***): Yellow solid; mp 134–136°C; IR (KBr): 1735, 1632, 1039, 760 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 2.36 (s, 3H); 5.93 (s, 2H); 6.71 (s, 1H); 7.10 (d, 2H, J = 7.6 Hz); 7.13 (s, 1H); 7.32 (s, 1H); 7.39 (d, 2H, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 25.1, 99.0, 102.3, 110.9, 113.0, 122.1, 125.6, 127.9, 129.4, 131.7, 132.3, 144.7, 147.7, 153.8, 163.1. MS (EI): m/z = 280 [M^+]. Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32%. Found: C, 73.01; H, 4.25%.

2.2v *3-Phenylpyrano[3,4-b]indol-1(9H)-one* (***2v***): Yellow solid; mp 171–173°C; IR (KBr): 3401, 2921, 1686, 742 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + DMSO-d_6): δ_H 7.13 (t, 1H, J = 6.8 Hz); 7.17–7.19 (m, 1H); 7.27 (d, 1H, J = 6.8 Hz); 7.34–7.37 (m, 3H); 7.39 (s, 1H); 7.45–7.50 (m, 1H); 7.79 (d, 1H, J = 7.6 Hz); 7.84 (d, 1H,J = 7.6 Hz); 11.94 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6): δ_C 97.7, 113.4, 120.8, 121.4, 121.9, 124.3, 124.8, 125.6, 127.7, 128.9, 129.0, 132.8, 140.6, 151.9, 157.0. MS (EI): m/z = 261 [M^+]. Anal. Calcd for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 78.39; H, 4.19; N, 5.26%.

2.2w *9-Methyl-3-phenylpyrano[3,4-b]indol-1(9H)-one* (***2w***): Yellow solid; Mp 168–170°C; IR (KBr): 1711, 1471, 1222, 1063, 742 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, variable temperature): δ_H 4.02 (s, 3H); 7.22–7.23 (m, 1H); 7.36–7.56 (m, 5H); 7.81–7.85 (m, 3H); 8.02–8.04 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6, variable temperature): δ_C 31.6, 98.3, 111.6, 120.9, 121.2, 121.4, 122.3, 124.8, 125.6, 128.3, 129.4, 129.5, 132.6, 141.5, 151.6, 156.1. MS (EI): m/z = 275 [M^+]. Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.69; H, 4.72; N, 5.03%.

2.2x *9-Ethyl-3-phenylpyrano[3,4-b]indol-1(9H)-one* (***2x***): Orange solid; mp 70–75°C; IR (neat): 1712, 1469, 1220, 1061, 739 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 1.44 (t, 3H, J = 7.6 Hz); 4.66 (q, 2H, J = 7.6 Hz); 7.24 (t, 1H, J = 6.9 Hz); 7.29 (s, 1H); 7.35 (d, 1H, J = 6.9 Hz); 7.41–7.43 (m, 3H); 7.49 (t, 1H, J = 6.9 Hz); 7.85–7.89 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 15.9, 39.6, 97.1, 110.7, 120.4, 120.9, 121.4,

121.7, 124.9, 125.9, 127.9, 128.8, 129.1, 132.6, 140.4, 152.4, 156.5. MS (EI): $m/z = 289$ [M^+]. Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.00; H, 4.28; N, 5.41%.

2.3 *Animals and drug dosage*

2.3a *Animals*: The selection of animals, caring and handling was done as per the guidelines set by the Indian National Science Academy, New Delhi, India. Inbred albino mice (Swiss strain) of adult gender weighing 120–150 g were used for the study. The mice were housed individually in clean polypropylene cages containing sterile paddy husk (procured locally) as bedding throughout the experiment. All animals were fed with sterile commercial pelleted rat chow supplied by Hindustan Lever Ltd (Mumbai, India) with free access to water (*ad libitum*) under standardized housing conditions (natural light-dark cycle, temperature 23 ± 1°C, relative humidity 55 ± 5%). After 7 days of adaptation to laboratory conditions, the animals were randomly assigned to 12 experimental groups of 5 mice each. Each mouse was used only once. All tests were performed between 08:00 and 16:00 h. All efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data. The experimental protocols and procedures listed below conformed to the Guide for the Care and Use of Laboratory Animals and approved by the Institutional Ethics Committee. Mice equivalent doses in mg/kg body weight of clinical doses were calculated as mg/kg body weight with the help of standard tables (Karber's method).[36] The test compounds were tested in mice after 14 days of administration for their safety as per OECD guidelines.[37] Experimental procedure for the evaluation of antinociceptive and antiinflammatory activities was discussed in sections 3.2 and 3.3, respectively.

2.4 *Dose and administration of compounds*

For the antinociceptive study, the target compounds (20 mg/kg), pentazocine as reference drug (20 mg/kg) and 2% (w/v) gum acacia (2 mL/kg) as control were administered orally by intragastric tube. For the anti-inflammatory study, the target compounds (20 mg/kg), indomethacin as reference drug (20 mg/kg) and 0.5% (w/v) tween 80 (2 mL/kg) as control were administerd orally.

2.5 *Statistical analysis*

The obtained data were analysed using one-way analysis of variance (ANOVA) followed by Dunnet's multiple comparison test using computerized Graph Pad Instat version 3.05 (Graph Pad software, USA). The results are presented as mean ± Standard error of means (SEM). Differences between data sets were considered as significant when $P < 0.001$.

3. Results and discussion

3.1 *Chemistry*

2-(Phenylethynyl)benzamide **1a**, which can easily be synthesized by the Sonogashira cross-coupling of 2-iodobenzamide with phenylacetylene,[38] was selected as a model substrate for the optimization of the reaction conditions. Several points regarding the optimization of conversion of **1a** to **2a** are worth noting. (i) No effort was made to exclude air or moisture in these experiments. (ii) Toluene was chosen as the solvent, since toluene is immiscible in HOTf at room temperature and forms a top-layer that avoids the evolution of toxic fumes during addition.[39] Thus, the reaction of 2-(phenylethynyl)benzamide **1a** with HOTf (1.0 equiv) in toluene at a microwave irradiation (300 W) for 30 min with 30 s pulse[40] showed an excellent and clean conversion toward 3-phenylisocoumarin[41] which was isolated in 80% yield after aqueous work-up followed by column chromatography.[42] Decreasing the amount of HOTf from 1.0 to 0.5 equiv resulted in product formation albeit in moderate yield (60%). Since 1.0 equiv of HOTf at a power level of 300 W was effective for the synthesis of isocoumarin **2a**, we were interested to apply this reaction condition for other substrates. The requisite starting materials **1a–n** were synthesized as outlined in scheme 1 and the results were presented in table 1.

Under this optimized condition all substrates underwent the reaction smoothly affording the products **2a–n** in good to excellent yields. Substrates with both electron releasing as well as withdrawing groups were tolerated under this reaction condition. Moreover, all the substrates gave isocoumarin as the exclusive product and no phthalide regioisomer was formed.[43] It was reasoned that traces of water present in triflic acid effects the hydrolysis of amide.[44] Irrespective of the nature of the substrates, the cyclization follows highly selective 6-*endo-dig* regiochemistry, which has been previously observed by Uchiyama *et al.*[9]

In view of the pharmacological significance of isocoumarins[45] and their prevalence as substructure in numerous natural products,[46] we extended our study to structurally diverse acetylenic amides bearing polyaromatic (schemes 2 and 3) and heteroaromatic (scheme 4) function and the results were given in table 2. Upon

Table 1. HOTf promoted synthesis of isocoumarins (**2a**–**2n**).

Entry	R	R^1	R^2	R^3	Product[a]	Yield (%)[b]
1	Ph	H	H	H	**2a**	80
2	*m*-F-ph	H	H	H	**2b**	71
3	*p*-anisyl	H	H	H	**2c**	81
4	*n*-Bu	H	H	H	**2d**	82
5	*n*-hexyl	H	H	H	**2e**	81
6	Ph	NO_2	H	H	**2f**	69
7	*p*-tolyl	NO_2	H	H	**2g**	70
8	*p*-anisyl	NO_2	H	H	**2h**	71
9	Ph	H	MeO	H	**2i**	77
10	*p*-anisyl	H	MeO	H	**2j**	83
11	Ph	H	H	MeO	**2k**	79
12	Et	H	MeO	H	**2l**	85
13	Me	H	MeO	H	**2m**	91
14	Et	H	H	F	**2n**	88

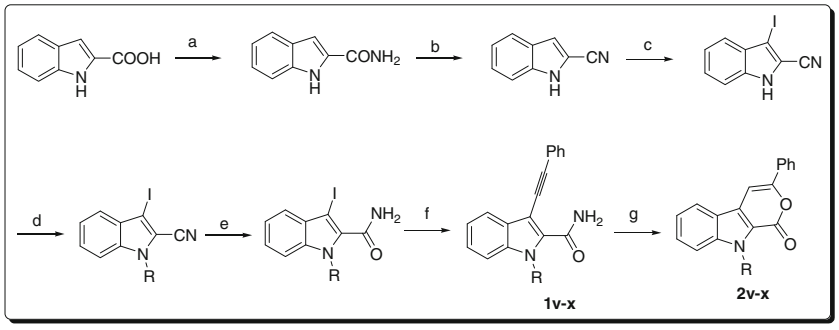
[a]All products were characterized by IR, NMR and mass spectroscopy
[b]Isolated yield

examining the fate of a variety of 3-ethynylnaphthalene-2-carboxamides **1o–r** under our reaction condition, we found that these substrates underwent the reaction smoothly providing excellent yield of products **2o–r**. The high yield obtained in these substrates could be attributed to the presence of naphthalene ring which enhances the electron density of the triple bond, thus interacts with the Brønsted acid with ease (entries 1–4, table 2).

The utility of our methodology is further manifested by its applicability to piperanol tethered benzamides **1s–u** (scheme 3). The reaction, indeed afforded the desired isocoumarin derivatives **2s–u** in yields ranging from 44% to 61%. The low yields in these cases **2s–u** was due to the partial decomposition of the corresponding substrates under the strong acidic conditions. However, we were not able to isolate the decomposed products, because of their sticky nature.

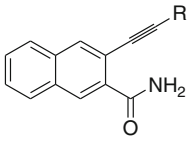
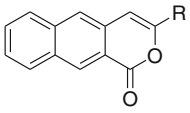
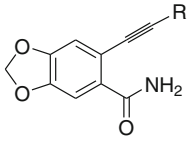
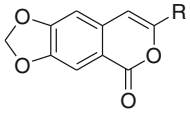
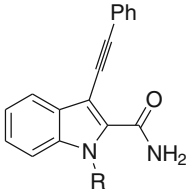
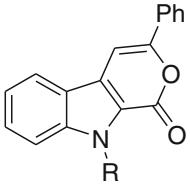
Our desire for the low molecular weight indole molecules led us to briefly investigate the fate of 3-(ethynyl)indole-2-carboxamides **1v–x** under the optimized reaction condition (scheme 4). The requisite starting materials were synthesized by standard literature procedures.[47] Only modest yields were observed for these substrates compared to other examples. Nevertheless, it is noteworthy to mention that similar substrates afforded no cyclization product at all under halocyclization conditions,[13a] thus highlighting the significance of our protocol.

The structure of all products was confirmed by spectral data (FTIR, ^{1}H NMR, ^{13}C NMR and EI-MS) and elemental analyses. The presence of absorption



Scheme 4. Reagents and condition: (a) 3.0 equiv. $SOCl_2$, Et_2O, 0 to 5°C, 1 h then excess NH_3 (aq.), 0°C to rt, 2 h; (b) 5.0 equiv. $POCl_3$, 100°C, 30 min; (c) 1.1 equiv. I_2/DMF, rt, 3 h; (d) 2.0 equiv. NaH, DMF, 30 min at 0°C then 3.0 equiv. RX, 0°C to rt, 6 h; (e) 30% H_2O_2/3.0 equiv. Na_2CO_3, DMSO, 5°C to rt, 1 h; (f) 5 mol% $Pd(PPh_3P)_2Cl_2$/5 mol% CuI/Et_3N, rt, 15 min, N_2 then 1.1 equiv. phenylacetylene (for substrate **1v**, no *N*-alkylation was carried out, thus R = H); (g) 1.0 equiv. TfOH, toluene, 300 W, 3 min.

Table 2. HOTf promoted synthesis fused pyranones (**2o–2x**).

Entry	Substrate	R	Product[a]	R	Yield (%)[b]
1		Ph **1o**		Ph **2o**	93
2		*n*-Bu **1p**		*n*-Bu **2p**	90
3		*p*-Tolyl **1q**		*p*-Tolyl **2q**	95
4		*o*-Tolyl **1r**		*o*-Tolyl **2r**	94
5		Ph **1s**		Ph **2s**	50
6		*n*-Bu **1t**		*n*-Bu **2t**	44
7		*p*-Tolyl **1u**		*p*-Tolyl **2u**	61
8		H **1v**		H **2v**	45
9		Me **1w**		Me **2w**	54
10		Et **1x**		Et **2x**	55

[a]All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy
[b]Isolated yield

at 1686–1744 cm^{-1} in the IR spectra of these compounds suggested a δ-lactone ring. ^{1}H NMR spectra of the compounds exhibited a sharp distinct singlet at δ_H 6.24–7.79 characteristic of C4-H of isocoumarin. Had it been γ-lactone, an absorption peak between 1770 and 1800 cm^{-1} and singlet at δ_H (vinylic) 5.0–7.0 ppm would be found in their IR and ^{1}H NMR spectra, respectively.[48] In ^{13}C NMR spectrum the lactone carbonyl and C4-carbon resonated at δ_C 156.1–165.2 and 97.1–104.1 ppm, respectively. All these spectral values confirmed the formation of products.

4. Pharmacology

4.1 *Evaluation of oral toxicity*

In the present study, all the synthesized compounds were screened for their *in vivo* antinociceptive and anti-inflammatory activities. To begin with, the oral toxicity of the synthesized compounds was performed by acute toxic class method[36] in accordance with the OECD guidelines.[37] The selected adult albino rats were fasted overnight prior to the acute experimental procedure. Following the period of fasting, the animals were weighed and the test compounds were orally administered at a dose of 20 mg/kg body weight. Immediately after dosing, the animals were observed for the first 30 min for behavioural changes and for mortality on a daily basis for a total of 14 days. There was no change in the haematological parameters and organ weights of drug treated animals compared to control. Histopathological examination of internal organs did not show any pathological changes. As no mortality was observed with the above dose, the LD_{50} value of the title compounds was expected to exceed 20 mg/kg of body weight. Toxicity assays showed that all the compounds proved to be non-toxic at the tested dose levels and well-tolerated by the experimental animals as their LD_{50} cut-off values >20 mg/kg body weight. However, we believe that detailed toxicological investigations are required to elucidate their chronic activity.

4.2 *Evaluation of antinociceptive activity*

Tail immersion method was used to evaluate the antinociceptive activity in male albino rats (Swiss strain) weighing 120–150 g.[49] Initially, the animals were screened for the sensitivity test by immersing the tail of the mice gently in hot water maintained at 55 ± 5°C. The animal immersing the tail from hot water with in 5 s was selected for the study. The animals were divided into 3 groups of 6 each. All the test compounds and standard drug were administered orally by intragastric tube. Group I was kept as control, receiving 2% w/v of gum acacia (2 mL/kg) in normal saline manner. Group II was kept as standard, receiving pentazocine (20 mg/kg). Group III was kept as test, receiving synthesized compounds (20 mg/kg). After administration of drugs, the animals react by withdrawing its tail. This reaction was determined before oral feeding of the standard drug and test compounds which were recorded as zero minutes reading. The time (in seconds) to

withdraw the tail clearly out of water was taken as the reaction time. The first reading (0 min) was taken immediately after the administration of the test compound and subsequent reaction time was recorded at 30, 60, 90 and 120 min, respectively. The mean reaction time was recorded for each group and compared with the value of the standard drug pentazocine. The percentage antinociceptive activity was calculated using the formula: % Antinociceptive activity $= \left[(T_2 - T_1)/T_2\right] \times 100$, where T_1 is the reaction time (in s) before treatment and T_2 is the reaction time (in s) after treatment. The mean value ± SEM was calculated for each parameter. The results were analysed statistically by ANOVA is followed by Dunnet's test. The results of the experiment by proper statistical analysis are tabulated in table 3, which revealed that all the tested compounds showed significant potency (44.24% to 83.16%) as compared to the standard drug pentazocine (84.81%) at 120 min. Among the isocoumarins, compounds having 3-hexyl **2e** and 3-anisyl, 4-MeO substituents **2j** showed enhanced activity compared to other derivatives of the same series. A markedly improved potency was observed when a lipophilic naphthalene system was fused with the pyranone ring **2o–r**. Replacement of naphthalene ring by a piperanal ring **2s–u** resulted in the significant decrease of activity. It was observed that pyranoindolones **2v–x** showed highest activity with values comparable to or slightly lesser than the standard pentazocine. Nevertheless, it is worth to mention that other compounds exhibited moderate to good antinociceptive activity.

4.3 *Evaluation of antiinflammatory activity*

The carrageenan-induced paw edema model in rats is known to be sensitive to cyclooxygenase inhibitors and has been used to evaluate the effect of non-steroidal antiinflammatory agents, which primarily inhibit the cyclooxygenase involved in prostaglandin synthesis.[50] In the present study, the antiinflammatory activity was determined by carrageenan-induced rat paw edema method in male albino rats (Swiss strain) weighing 120–150 g.[51] The animals were divided into 3 groups of 6 each. All the test compounds and reference drug were administered orally, suspended in 0.5% aqueous solution of Tween 80 (polyoxyethylene sorbitan mononucleate) solution. Group I was kept as control,

Table 3. Antinoceceptive activity of synthesized compounds by tail immersion test.

Entry	Treatments	Dose levels	Tail immersion response in seconds (mean ± SEM)					% Antinoceceptive activity			
			0 min	30 min	60 min	90 min	120 min	30 min	60 min	90 min	120 min
1	**2a****	20 mg/kg	2.98 ± 0.02	2.04 ± 0.01	1.80 ± 0.01	1.59 ± 0.01	1.28 ± 0.01	32.89	40.78	47.52	57.75
2	**2b***	20 mg/kg	2.99 ± 0.01	2.09 ± 0.01	1.93 ± 0.01	1.77 ± 0.01	1.60 ± 0.01	31.25	36.51	41.58	47.19
3	**2c****	20 mg/kg	2.99 ± 0.01	2.03 ± 0.02	1.77 ± 0.01	1.57 ± 0.01	1.26 ± 0.01	33.22	41.77	48.18	58.41
4	**2d***	20 mg/kg	3.00 ± 0.02	2.01 ± 0.01	1.72 ± 0.01	1.51 ± 0.02	1.22 ± 0.01	33.88	43.42	50.16	59.73
5	**2e****	20 mg/kg	2.98 ± 0.03	1.98 ± 0.01	1.69 ± 0.01	1.48 ± 0.02	1.20 ± 0.01	34.86	44.40	51.15	60.39
6	**2f****	20 mg/kg	2.99 ± 0.01	2.13 ± 0.01	1.93 ± 0.01	1.77 ± 0.01	1.61 ± 0.01	30.03	36.51	41.58	46.86
7	**2g****	20 mg/kg	2.98 ± 0.01	2.16 ± 0.02	1.97 ± 0.01	1.80 ± 0.01	1.64 ± 0.01	28.94	35.19	40.59	45.87
8	**2h****	20 mg/kg	2.98 ± 0.01	2.20 ± 0.01	2.00 ± 0.01	1.85 ± 0.03	1.69 ± 0.01	27.63	34.21	38.94	44.24
9	**2i***	20 mg/kg	2.99 ± 0.01	2.01 ± 0.02	1.76 ± 0.01	1.55 ± 0.01	1.24 ± 0.01	33.88	42.10	48.84	59.07
10	**2j****	20 mg/kg	2.97 ± 0.02	1.99 ± 0.01	1.67 ± 0.01	1.47 ± 0.01	1.19 ± 0.02	34.53	45.06	51.48	60.72
11	**2k****	20 mg/kg	2.98 ± 0.02	2.02 ± 0.02	1.78 ± 0.01	1.58 ± 0.01	1.25 ± 0.01	33.55	41.44	47.85	58.74
12	**2l****	20 mg/kg	2.98 ± 0.02	2.02 ± 0.01	1.74 ± 0.01	1.52 ± 0.02	1.23 ± 0.01	33.55	42.76	49.83	59.40
13	**2m****	20 mg/kg	2.97 ± 0.00	2.03 ± 0.01	1.75 ± 0.01	1.53 ± 0.02	1.24 ± 0.02	33.22	42.43	49.50	59.07
14	**2n***	20 mg/kg	2.99 ± 0.01	2.06 ± 0.01	1.90 ± 0.01	1.74 ± 0.01	1.58 ± 0.01	32.23	37.50	42.57	47.85
15	**2o****	20 mg/kg	2.98 ± 0.02	1.79 ± 0.01	1.51 ± 0.01	1.25 ± 0.01	1.02 ± 0.01	41.11	50.32	58.74	66.36
16	**2p****	20 mg/kg	2.98 ± 0.02	1.78 ± 0.01	1.50 ± 0.01	1.22 ± 0.01	1.00 ± 0.01	41.44	50.65	59.73	66.99
17	**2q****	20 mg/kg	2.98 ± 0.02	1.72 ± 0.02	1.48 ± 0.01	1.17 ± 0.01	0.97 ± 0.01	43.42	51.31	61.38	67.98
18	**2r****	20 mg/kg	2.98 ± 0.01	1.75 ± 0.01	1.49 ± 0.01	1.20 ± 0.01	1.01 ± 0.01	42.43	50.98	60.39	66.66
19	**2s****	20 mg/kg	3.01 ± 0.02	2.03 ± 0.01	1.79 ± 0.01	1.58 ± 0.01	1.27 ± 0.01	33.22	41.11	47.85	58.08
20	**2t****	20 mg/kg	2.99 ± 0.03	2.11 ± 0.02	1.84 ± 0.01	1.63 ± 0.01	1.31 ± 0.01	30.59	39.47	46.20	56.76
21	**2u****	20 mg/kg	3.00 ± 0.01	2.15 ± 0.01	1.89 ± 0.01	1.69 ± 0.01	1.36 ± 0.01	29.27	37.82	44.22	55.26
22	**2v****	20 mg/kg	3.01 ± 0.02	1.69 ± 0.02	1.28 ± 0.03	0.99 ± 0.01	0.57 ± 0.01	44.40	57.15	67.32	81.18
23	**2w****	20 mg/kg	3.02 ± 0.01	1.60 ± 0.01	1.17 ± 0.02	0.92 ± 0.01	0.55 ± 0.01	47.36	61.51	69.63	81.84
24	**2x****	20 mg/kg	3.03 ± 0.02	1.50 ± 0.02	1.08 ± 0.03	0.85 ± 0.03	0.51 ± 0.02	50.65	64.44	71.94	83.16
25	Gum acacia[a]	2 mL/kg	3.00 ± 0.01	3.04 ± 0.01	3.04 ± 0.01	3.03 ± 0.02	3.03 ± 0.01	–	–	–	–
26	Pentazocine	20 mg/kg	1.71 ± 0.01	1.42 ± 0.02	1.00 ± 0.03	0.78 ± 0.03	0.46 ± 0.02	53.28	67.10	74.25	84.81

[a]2.0% (w/v) of gum acacia was used as control
Data were analysed by one way ANOVA followed by Dunnet's test
*significant, P value <0.05; **highly significant, P value <0.001
SEM: Standard error of means

receiving 0.5% Tween solution. Group II was kept as standard, receiving indomethacin (20 mg/kg, p.o). Group III was kept as test, receiving synthesized compounds (20 mg/kg). After 30 min, carrageenan solution (0.1% in sterile 0.9% NaCl solution) in a volume of 0.1 mL was injected into the lateral malleolus of the sub-plantar region of the right hind paw of control as well as drug treated animals. The right hind paw volume was measured before and after carrageenan injection at various intervals (30, 60, 90 and 120 min) using digital plethysmometer. The percentage antiinflammatory activity was calculated according to the following formula: % Antiinflammatory activity $= \left(1 - \mathrm{Vt}/\mathrm{Vc}\right) \times 100$, where Vt represents the mean in paw volume in rats tested with test compounds and Vc represents the mean increase in paw volume in control group of rats. Data are expressed as mean ± SEM. The student *t*-test was applied to determine the significance of the difference between the control group and rats treated with the test compounds. The antiinflammatory activity of the 24 test compounds **2a**–**x** was compared with the standard drug indomethacin (table 4). At the same oral dose, indomethacin showed 77.91% inhibition of rat paw edema, whereas the tested compounds showed inhibition ranging from 9.69 to 73.93% after 120 min. The results clearly indicate that among all the compounds, the indole derivatives **2v**–**x** potentially migrated the carrageenan-induced inflammation in rats and emerged as the most active compounds (69.69%, 70.30% and 73.93% inhibition, respectively). When the pyranone system with different substituents at C-3 position is fused with a piperanol ring **2s**–**u**, moderate potency was observed and emerged as the second most active series. Replacement of piperanal moiety by a lipophilic naphthalene ring **2o**–**r** showed considerable decrease in activity. Finally, isocoumarins with different peripheral substituents but devoid of any heterocyclic core **2a**–**n** exhibited minimal antiinflammatory effect compared to other series. Among the peripheral substituents the nitro group **2f**–**h** was well-tolerated and offers enhanced activity over other substituents. A markedly reduced potency was observed when an alkyl chain is placed at the C-3 position **2d**, **2e**, **2l** and **2m**. It is our belief that molecular docking studies are required to study the hydrophobic interactions between the various atoms of the targeted compounds and aminoacid residues of the COX-II receptor, thus to reason out the observed activity.

Table 4. Antiinflammatory activity of synthesized compounds by carrageenan-induced paw edema method.

Entry	Treatments	Dose levels	Increase in paw volume (mean ± SEM)					% Antiinflammatory activity			
			0 min	30 min	60 min	90 min	120 min	30 min	60 min	90 min	120 min
1	**2a****	20 mg/kg	1.66 ± 0.01	1.50 ± 0.01	1.46 ± 0.02	1.41 ± 0.02	1.35 ± 0.01	09.68	12.04	14.54	18.18
2	**2b***	20 mg/kg	1.66 ± 0.02	1.49 ± 0.01	1.42 ± 0.01	1.34 ± 0.03	1.29 ± 0.01	10.24	14.45	18.78	21.81
3	**2c****	20 mg/kg	1.66 ± 0.01	1.52 ± 0.01	1.47 ± 0.02	1.42 ± 0.02	1.36 ± 0.01	08.40	11.44	13.93	17.57
4	**2d****	20 mg/kg	1.66 ± 0.02	1.58 ± 0.02	1.53 ± 0.01	1.50 ± 0.01	1.47 ± 0.01	04.81	07.83	09.09	10.90
5	**2e****	20 mg/kg	1.66 ± 0.02	1.59 ± 0.02	1.55 ± 0.01	1.52 ± 0.01	1.49 ± 0.01	04.21	06.62	07.87	09.69
6	**2f****	20 mg/kg	1.65 ± 0.01	1.35 ± 0.02	1.29 ± 0.01	1.25 ± 0.01	1.21 ± 0.01	18.78	22.28	24.24	26.66
7	**2g***	20 mg/kg	1.66 ± 0.02	1.39 ± 0.02	1.33 ± 0.01	1.27 ± 0.01	1.24 ± 0.01	16.26	19.87	23.03	24.84
8	**2h****	20 mg/kg	1.66 ± 0.02	1.36 ± 0.02	1.31 ± 0.01	1.26 ± 0.01	1.22 ± 0.01	18.07	21.08	23.63	26.06
9	**2i***	20 mg/kg	1.66 ± 0.01	1.50 ± 0.02	1.47 ± 0.01	1.45 ± 0.02	1.37 ± 0.02	09.63	11.44	12.12	16.96
10	**2j****	20 mg/kg	1.66 ± 0.01	1.56 ± 0.02	1.51 ± 0.01	1.48 ± 0.01	1.44 ± 0.01	06.02	09.03	10.30	12.72
11	**2k***	20 mg/kg	1.66 ± 0.01	1.51 ± 0.01	1.48 ± 0.02	1.44 ± 0.02	1.36 ± 0.02	08.97	10.84	12.72	18.07
12	**2l****	20 mg/kg	1.65 ± 0.01	1.55 ± 0.02	1.50 ± 0.01	1.47 ± 0.01	1.45 ± 0.01	06.62	09.09	10.90	12.12
13	**2m****	20 mg/kg	1.66 ± 0.02	1.54 ± 0.02	1.49 ± 0.01	1.46 ± 0.01	1.44 ± 0.02	07.22	10.24	11.44	12.72
14	**2n***	20 mg/kg	1.66 ± 0.01	1.47 ± 0.02	1.40 ± 0.01	1.33 ± 0.01	1.28 ± 0.01	11.44	15.66	19.87	22.42
15	**2o****	20 mg/kg	1.64 ± 0.02	1.34 ± 0.02	1.30 ± 0.01	1.24 ± 0.01	1.19 ± 0.01	19.27	21.68	24.84	27.87
16	**2p****	20 mg/kg	1.66 ± 0.01	1.40 ± 0.02	1.37 ± 0.01	1.29 ± 0.01	1.25 ± 0.02	15.66	17.46	21.81	24.24
17	**2q****	20 mg/kg	1.66 ± 0.01	1.37 ± 0.02	1.33 ± 0.01	1.27 ± 0.01	1.22 ± 0.02	17.46	19.69	23.03	26.06
18	**2r***	20 mg/kg	1.66 ± 0.01	1.35 ± 0.02	1.31 ± 0.01	1.25 ± 0.01	1.20 ± 0.02	18.67	21.08	24.24	27.27
19	**2s****	20 mg/kg	1.65 ± 0.02	1.20 ± 0.01	1.01 ± 0.01	0.93 ± 0.02	0.73 ± 0.01	27.71	39.15	43.80	55.75
20	**2t****	20 mg/kg	1.66 ± 0.01	1.25 ± 0.01	1.07 ± 0.01	1.00 ± 0.02	0.80 ± 0.01	24.69	35.54	39.39	51.51
21	**2u****	20 mg/kg	1.66 ± 0.02	1.24 ± 0.01	1.02 ± 0.01	0.98 ± 0.02	0.76 ± 0.01	25.30	38.55	40.60	53.93
22	**2v****	20 mg/kg	1.64 ± 0.02	0.95 ± 0.01	0.77 ± 0.03	0.64 ± 0.03	0.50 ± 0.01	42.77	53.61	61.21	69.69
23	**2w****	20 mg/kg	1.65 ± 0.02	0.92 ± 0.01	0.75 ± 0.01	0.63 ± 0.03	0.49 ± 0.01	44.57	54.81	61.81	70.30
24	**2x****	20 mg/kg	1.64 ± 0.02	0.99 ± 0.01	0.79 ± 0.01	0.68 ± 0.03	0.43 ± 0.01	40.36	52.40	58.78	73.93
25	Tween 80[a]	2 mL/kg	1.67 ± 0.01	1.66 ± 0.01	1.66 ± 0.01	1.65 ± 0.02	1.65 ± 0.02	–	–	–	–
26	Indomethacin	20 mg/kg	1.58 ± 0.01	1.19 ± 0.03	0.91 ± 0.04	0.55 ± 0.03	0.36 ± 0.02	28.31	45.18	66.6	77.91

[a]0.5% (w/v) of Tween 80 was used as control
Data were analysed by one way ANOVA followed by Dunnet's test
*significant, *P* value <0.05; **highly significant, *P* value <0.001
SEM: Standard error of means

5. Conclusion

We have reported here a brief investigation on the sequential hydrolysis/cycloisomerization of *o*-(alkynyl)benzamides with triflic acid under microwave condition. This methodology has allowed us to construct substituted isocoumarins in a regioselective manner. To the best of our knowledge, these are the first examples of direct synthesis of isocoumarins from *o*-(alkynyl)benzamides under super acid catalysis. This chemistry significantly broadens the synthetic utility of *o*-(alkynyl)benzamides and highlights the ability of triflic acid to operate two dissimilar reactions in the same reaction flask. The biological potential of the synthesized compounds were evaluated for their antinociceptive and antiinflammatory activities using *in vivo* rodent models, which indicate a comparable activity against the reference drugs. The biological evaluation led to the finding that pyranone fused with indole rings exhibited excellent antinociceptive as well as antiinflammatory activities. Studies addressed toward the application of this methodology to natural products and identification of reaction intermediates using deuterium labelling experiments are under investigation.

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References

1. Howells R D and McCown J D 1977 *Chem. Rev.* **77** 69
2. Stang P J and White M R 1983 *Aldrichimica Acta* **16** 15
3. (a) Puglici A, Lee A-L, Schrock R R and Hoveyda A H 2006 *Org. Lett.* **8** 1871; (b) Bennasar M-L, Zulaica E and Tummers S 2004 *Tetrahedron Lett.* **45** 6283
4. Haszeldine R N and Kidd J M 1954 *J. Chem. Soc.* 4228
5. Gramstad T and Haszeldine R N 1956 *J. Chem. Soc.* 173
6. (a) Dumeunier R and Markó I E 2004 *Tetrahedron Lett.* **45** 825; (b) Loh T-P, Hu Q-Y and Ma L-T 2002 *Org. Lett.* **4** 2389; (c) Olah G A, Wu A-h 1991 *Synthesis* 407; (d) Rosenfeld D C, Shekhar S, Takemiya A, Utsunomiya M and Hartwig J F 2006 *Org. Lett.* **8** 4179; (e) Villemin D, Bar N and Hammadi M 1997 *Tetrahedron Lett.* **38** 4777; (f) Abid M, Teixeira L and Török B 2007 *Tetrahedron Lett.* **48** 4047; (g) Li Z, Zhang J, Brouwer C, Yang C-G, Reich N-W and He C 2006 *Org. Lett.* **8** 4175; (h) Elford T G, Arimura Y, Yu S H and Hall D G 2007 *J. Org. Chem.* **72** 1276; (i) Abid M, Teixeira L and Török B 2008 *Org. Lett.* **10** 933; (j) Corey E J, Shibata T and Lee T W 2002 *J. Am. Chem. Soc.* **124** 3808; (k) Koltunov K Y 2007 *Tetrahedron Lett.* **48** 5631; (l) Reddy B V S, Ramesh K, Ganesh A V, Kumar G G K S N, Yadav J S and Grée R 2011 *Tetrahedron Lett.* **52** 495; (m) Jin T, Uchiyama J, Himuro M and Yamamoto Y 2011 *Tetrahedron Lett.* **52** 2069; (n) Safina L Y, Selivanova G A, Koltunov K Y and Shteingarts V D 2009 *Tetrahedron Lett.* **50** 5245; (o) Li A, DeSchepper D J and Klumpp D A 2009 *Tetrahedron Lett.* **50** 1924; (p) Bodnar B S and Miller M J 2009 *Tetrahedron Lett.* **50** 796; (q) Mendoza O, Rossey G and Ghosez L 2011 *Tetrahedron Lett.* **52** 2235; (r) Klumpp D A, Zhang Y, Kindelin P J and Lau S 2006 *Tetrahedron* **62** 5915; (s) Klumpp D A, Yeung K Y, Prakash G K S and Olah G A 1998 *J. Org. Chem.* **63** 4481; (t) Yamamoto Y, Gridnev I D, Patil N T and Jin T 2009 *Chem. Commun.* 5075
7. Ramsden C A, Scriven E F V and Taylor R J K 2008 *Comprehensive heterocyclic chemistry*, III edition; New York: Elsevier
8. (a) Bunin B A 1998 *The combinatorial index*; London: Academic Press; (b) Obrecht D and Villalgordo J M 1998 *Solid-supported combinatorial and parallel synthesis of small-molecular-weight compound libraries*; Elsevier; (c) In: *Combinatorial chemistry: Synthesis, analysis, screening*; Jung G, Ed.; Weinheim: Wiley-VCH 1999; (d) *Combinatorial chemistry and molecular diversity in drug discovery*; E M Gordon and J F Kerwin Jr (eds); New York: John Wiley & Sons 1998
9. Uchiyama M, Ozawa H, Takuma K, Matsumoto Y, Yonehara M, Hiroya K and Sakamoto T 2006 *Org. Lett.* **8** 5517
10. Bianchi G, Chirani M, Marinelli F, Rossi L and Arcadi A 2010 *Adv. Synth. Catal.* **352** 136
11. Roy S, Roy S, Neuenswander B, Hill D and Larock R C 2009 *J. Comb. Chem.* **11** 1128
12. (a) Praveen C, Dheenkumar P, Muralidharan D and Perumal P T 2010 *Bioorg. Med. Chem. Lett.* **20** 7292; (b) Praveen C, Kumar K H, Muralidharan D and Perumal P T 2008 *Tetrahedron* **64** 2369; (c) Praveen C, Parthasarathy K and Perumal P T 2010 *Synlett.* 1635; (d) Praveen C, Jegatheesan S and Perumal P T 2009 *Synlett* 2795; (e) Praveen C, Kalyanasundaram A and Perumal P T 2010 *Synlett* 777; (f) Praveen C, Sagayaraj Y W and Perumal P T 2009 *Tetrahedron Lett.* **50**, 644; (g) Praveen C, Kiruthiga P and Perumal P T 2009 *Synlett.* 1990; (h) Praveen C, Karthikeyan K and Perumal P T 2009 *Tetrahedron* **65** 9244; (i) Praveen C and Perumal P T 2011 *Synlett* 521; (j) Praveen C, Iyyappan C and Perumal P T 2010 *Tetrahedron Lett.* **51** 4767; (k) Praveen C, Ayyanar A and Perumal P T 2011 *Bioorg. Med. Chem. Lett.* **21** 4072; (l) Praveen C, Ayyanar A and Perumal P T 2011 *Bioorg. Med. Chem. Lett.* **21** 4170; (m) Balakrishnan B, Praveen C, Seshadri P R and Perumal P T 2011 *Acta Crystallogr.* **E67** o1575; (n) Praveen C, Iyyappan C, Girija K, Kumar K S and Perumal P T 2012 *J. Chem. Sci.* **124** 451; (o) Praveen C, Iyyappan C, Perumal P T and Girija K 2012 *Indian J. Chem. Soc.* **51B** 498; (p) Praveen C, Nandakumar A, Dheenkumar P, Muralidharan D and Perumal P T 2012 *J. Chem. Sci.* **124** 609
13. For the cyclization of 2-(alkynyl)benzamides to isoindolinones and isoquinolinones, see: (a) Yao T and Larock R C 2003 *J. Org. Chem.* **68** 5936; (b) Koseki

Y, Kusano S, Sakata H and Nagasaka T 1999 *Tetrahedron Lett.* **40** 2169; (c) Kundu N G, Khan M W and Mukhopadgyay R 1999 *Tetrahedron* **55** 12361; (d) Kundu N G, Khan M W 2000 *Tetrahedron* **56** 4777

14. For the cyclization of 2-(alkynyl)benzoic acids to isocoumarins and phthalides, see: (a) Mehta S Waldo J P and Larock R C 2009 *J. Org. Chem.* **74** 1141; (b) Yao T and Larock R C 2003 *J. Org. Chem.* **68** 5936; (c) Peuchmaur M, Lisowski V, Gandreuil C, Maillard L T, Martinez J and Hernandez J-F 2009 *J. Org. Chem.* **74** 4158; (d) Biagetti M, Bellina F, Carpita A, Stabilea P and Rossi R 2002 *Tetrahedron* **58** 5023; (e) Roy S, Roy S, Neuenswander B, Hill D and Larock R C 2009 *J. Comb. Chem.* **11** 1128; (f) Sakamoto T, An-Naka M, Kondo Y and Yamanaka H 1986 *Chem. Pharm. Bull.* **34** 2754; (g) Subramanian V, Batchu V R, Barange D and Pal M 2005 *J. Org. Chem.* **70** 4778; (h) Uchiyama M, Ozawa H, Takuma K, Matsumoto Y, Yonehara M, Hiroya K and Sakamoto T 2006 *Org. Lett.* **8** 5517; (i) Raju S, Batchu V R, Swamy N K, Dev R V, Sreekanth B R, Babu J M, Vyas K, Kumar P R, Mukkanti K, Annamalai P and Pal M 2006 *Tetrahedron* **62** 9554; (j) Sashida H, Kawamukai A 1999 *Synthesis* 1145; (k) Liao H-Y and Cheng C-H 1995 *J. Org. Chem.* **60** 3711; (l) Liang Y, Xie Y-X and Li J-H 2007 *Synthesis* 400; (m) Bras G L, Hamze A, Messaoudi S, Provot O, Calvez P-B L, Brion J-D and Alami M 2008 *Synthesis* 1607
15. For reviews highlighting the significance of microwave in organic transformations, see: (a) Caddick S 1995 *Tetrahedron* **51** 10403; (b) Lidström P, Tierney J, Wathney B and Westman J 2001 *Tetrahedron* **57** 9225; (c) Wathey B, Tierney J, Lidstrom P and Westman 2002 *J. Drug Discovery Today* **7** 373; (d) Alcázar J, Diels G and Schoentjes B 2007 *Comb. Chem. High Throughput Screening* **10** 918; (e) Caddick S and Fitzmaurice R 2009 *Tetrahedron* **65** 3325; (f) De la Hoz A, Díaz-Ortiz A and Moreno A 2005 *Chem. Soc. Rev.* **34** 164; (g) Galema S A 1997 *Chem. Soc. Rev.* **26** 233; (h) Rajak H and Mishra P 2004 *J. Sci. Ind. Res.* **63** 641
16. (a) Goldstein H and Grampoloff A V 1930 *Helvetica Chimica Acta* **13** 310; (b) Kenner J and Turner H A 1928 *J. Chem. Soc.* 2340; (c) Stanley W M, McMahon E and Adams R 1993 *J. Am. Chem. Soc.* **55** 706; (d) Harayama T and Shibaike K 1998 *Heterocycles* **49** 191
17. (a) Wu M-J, Chang L-J, Wei L-M and Lin C-F 1999 *Tetrahedron* **55** 13193; (b) Couture A, Grandclaudon P 1986 *Synthesis* 576
18. Yao T and Larock R C 2005 *J. Org. Chem.* **70** 1432
19. Kundu N G and Khan M W 2000 *Tetrahedron* **56** 4777
20. Travis B R, Sivakumar M, Hollist G O and Borhan B 2003 *Org. Lett.* **5** 1031
21. Doyle F P, Ferrier W, Holland D O, Mehta M D and Nayler J H C 1956 *J. Chem. Soc.* 2853
22. (a) Chashi T, Sada T, Fujimoto H, Nagayama C, Sugino E and Hibino S 1997 *J. Org. Chem.* **62** 2535; (b) Sakamoto T, Nagano T, Kondo Y and Yamanaka H 1988 *Chem. Pharm. Bull.* **36** 2248
23. (a) Dehaen W and Hassner A 1991 *J. Org. Chem.* **56** 896; (b) Tsotinis A, Afroudakis P A, Davidson K, Prashar A and Sugden D 2007 *J. Med. Chem.* **50** 6436; (c) Li C-F, Liu H, Liao J, Cao Y-J, Liu X-P and Xiao W-J 2007 *Org. Lett.* **9** 1847; (d) Sechi M, Derudas M, Dallocchio R, Dessí A, Bacchi A, Sannia L, Carta F, Palomba M, Ragab O, Chan C, Shoemaker R, Sei S, Dayam R and Neamati N 2004 *J. Med. Chem.* **47** 5298; (e) Forbes I T, Kennet G A, Gadre A, Ham P, Hayward C J, Martin R T, Thompson M, Wood M D, Baxter G S, Glen A, Murphy O E, Stewart B A and Blackburn T P 1993 *J. Med. Chem.* **38** 1104; (f) Kikugawa Y and Miyake Y A 1981 *Synthesis* 461; (g) Bergman J and Sand P 1993 *Tetrahedron* **43** 6085
24. Larock R C, Varaprath S, Lau H H, Fellows C A 1984 *J. Am. Chem. Soc.* **106** 5274
25. Marchal E, Uriac P, Legouin B, Toupet L and van de Weghe P 2007 *Tetrahedron* **63** 9979
26. Chin L-Y, Lee C-Y, Lo Y-H and Wu M-J 2008 *J. Chin. Chem. Soc.* **55** 643
27. (a) Batu G and Stevenson R 1980 *J. Org. Chem.* **45** 1532; (b) Liao H-Y and Cheng C-H 1995 *J. Org. Chem.* **60** 3711
28. Ohta S, Kamata Y, Inagaki T, Masuda Y, Yamamoto S, Yamashita M and Kawasaki I 1993 *Chem. Pharm. Bull.* **41** 1188
29. Woon E C Y, Dhami A, Mahon M F and Threadgill M D 2006 *Tetrahedron* **62** 4829
30. Elix J A and Murphy D P 1975 *Aust. J. Chem.* **28** 1559
31. Rossi R, Carpita A, Bellina F, Stabilea P and Mannina L 2003 *Tetrahedron* **59** 2067
32. Lewis C N, Spargo P L and Staunton J 1986 *Synthesis* 944
33. Cherry K, Parraim J-L, Thibonnet J, Duchêne A and Abarbri M 2005 *J. Org. Chem.* **70** 6669
34. Hauser F M, Dorsch W A and Mal D 2002 *Org. Lett.* **4** 2237
35. Miura M, Tsuda T, Satoh, Pivsa-Art S and Nomura M 1998 *J. Org. Chem.* **63** 5211
36. (a) Ghosh M N 2005 *Fundamentals of experimental pharmacology*, 3rd Edition, Kolkatta: Hilton and Co. 190–7; (b) Kale S R and Kale R R 1994 *Practical pharmacology and toxicology*, 1st Edition, Pune: Nirali Prakashan, 56
37. OECD 1987 *Guidelines for testing chemicals*, No. 401, Acute Oral Toxicity (Paris), 1
38. (a) Sonogashira K, Tohda Y and Hagihara N 1975 *Tetrahedron Lett.* **16** 4467; (b) Tykwinsky R R 2003 *Angew. Chem.* **115** 1604; (c) Tykwinsky R R 2003 *Angew. Chem. Int. Ed.* **42** 1566
39. It was expected that the evolution of toxic fumes of triflic acid could be somewhat controlled by using toluene which forms the top layer. For related discussion, see: Rombouts F, Franken D, Martínez-Lamenca C, Braeken M, Zavattaro C, Chen J and Trabanco A A 2010 *Tetrahedron Lett.* **51** 4815
40. No reaction was observed at room temperature
41. The physical and spectral data of the product matched with the literature value, see: ref. 23
42. Hydrolysis of benzamide to benzoic acid in excellent yield was achieved under similar conditions
43. For the cyclization of 2-(alkynyl)benzoic acids to both phthalides and isocoumarins, see: (a) Sakamoto T, An-naka M, Kondo Y and Yamanaka H 1986 *Chem. Pharm. Bull.* **34** 2754; (b) Sashida H and Kawamukai A 1999 *Synthesis* 1145; (c) Inack-Ngi S, Rahmani R,

Commeiras L, Chouraqui G, Thibonnet J, Duchêne A, Abarbri M and Parrain J-L 2009 *Adv. Synth. Catal.* **351** 779; (d) Kundu N G and Pal M J 1993 *Chem. Soc. Chem. Commun.* 86. Also see: ref. 24 and 30.

44. For discussion, see: (a) Li X and Liao S 2009 *J. Mol. Struct.* (THEOCHEM) **897** 66; (b) Olha G A; Batamack P, Deffieux D; Török B, Wang Q, Molnár A and Praksah G K S 1996 *Appl. Catal. A-Gen.* **146** 107
45. (a) Trani A, Dallanoce C, Panzone G, Ripamonti F, Goldstein B P and Ciabatti R 1997 *J. Med. Chem.* **40** 967; (b) Lee J H, Park Y J, Kim H S, Hong Y S, Kim K W and Lee J J 2001 *J. Antibiot.* **54** 463; (c) Matsuda H, Shimoda H, Yamahara J and Yoshikawa M 1998 *Bioorg. Med. Chem. Lett.* **8** 215
46. (a) Bauta W E, Lovett D P, Cantrell Jr W R and Burke B D 2003 *J. Org. Chem.* **68** 5967; (b) Whyte A C, Gloer J B, Scott J A and Mallock D 1996 *J. Nat. Prod.* **59** 765; (c) Furuta T, Fukuyama Y and Asakawa Y 1986 *Phytochemistry* **25** 517; (d) Yoshikawa M, Uchida E, Chatani N, Murakami N and Yamahara J 1992 *J. Chem. Pharm. Bull.* **40** 3121; (e) Yoshikawa M, Uchida E, Naitoh Y, Inoue K, Matsuda H, Shimoda H, Yamahara J and Murakami N 1994 *J. Chem. Pharm. Bull.* **42** 2225; (f) Yoshikawa M, Matsuda H, Shimoda H, Shimada H, Harada E, Naitoh Y, Miki A, Yamahara J and Murakami N 1996 *J. Chem. Pharm. Bull.* **44** 1440; (g) Bürki N, Michel A and Tabacchi R 2003 *Phytopathol. Mediterr.* **42** 191; (h) Xin Z-H, Li-Tian, Zhu T-J, Wang W-L, Du L, Fang Y-C, Gu Q-Q and Zhu W-M 2007 *Arch. Pharm. Res.* **30** 816
47. (a) Abramovitch R A and Cue B W Jr 1973 *Heterocycles* **1** 227; (b) Pletnev A A, Tian Q and Larock R C 2002 *J. Org. Chem.* **67** 9276
48. For discussion, see: Kundu N G, Pal M and Nandi B 1998 *J. Chem. Soc. Perkin Trans.* **1** 561
49. (a) Winter C A, Risley E A and Nuss G W 1963 *J. Pharmacol. Exp. Ther.* **141** 369; (b) Amir M, Kumar H and Khan S A 2008 *Bioorg. Med. Chem. Lett.* **18** 918; (c) Winter C A, Risley E A and Nuss G W 1962 *Proc. Soc. Exp. Biol. Med.* **111** 544
50. Seibert K, Zhang Y, Leahy K, Hauser S, Masferrer J, Perkins W, Lee L and Isakson P 1994 *Proc. Natl. Acad. Sci. USA* **91** 12013
51. Vogel H G 2002 *Drug discovery and evaluation—Pharmacological assays*, 2nd Edition, New York: Springer, 697