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TiO_2-Catalysed Synthesis of Hydrazinyl Thiazoles and their Evaluation for Anticancer Activity in MOC2 Cells

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A series of hydrazinyl thiazole derivatives were synthesised (**4a-j**) *via* an efficient titanium dioxide (TiO_2) catalysed protocol using 1-indanone, phenacyl bromide and thiosemicarbazide as key starting materials. All the synthesised compounds were fully characterised by ^1H NMR, ^{13}C NMR and mass spectral data. The developed methodology offers mild reaction conditions, good to excellent yield and operational simplicity, highlighting the catalytic efficiency of TiO_2. The synthesized compounds were also evaluated against MOC2 cell lines using the MTT assay as a preliminary *in vitro* screening tool to assess their anticancer activity, effects on cell viability, comparative efficacy, and structure–activity relationships. The obtained results were expressed with IC_{50} μM and **4f** was the most potent with an IC_{50} of 26.53 μM, followed by **4d** (30.48 μM) and **4h** (37.83 μM).

Keywords: Hydrazinyl thiazole derivatives, 1-Indanone, Anticancer activity, Phenacyl bromide, Thiosemicarbazide.

INTRODUCTION

Thiazoles are an important class of nitrogen- and sulfur-containing heterocycles that have attracted considerable attention due to their broad spectrum of biological activities, including antibacterial [1], anticancer [2], antiviral [3], antitumor [4], antifungal [5], antioxidant [6,7] and antimicrobial properties [8]. Beyond medicinal applications, thiazole derivatives have found utility as anti-corrosion agents [9], cosmetic ingredients [10], dyes [11], pigments [12] and agrochemicals [13]. The pharmacological significance of this scaffold is illustrated by several biologically active molecules including antimicrobial and anticancer agents (I and II) [14,15], the antifungal drug abafungin (III) [16], the clinically approved tyrosine kinase inhibitor dasatinib (IV) [17], anticancer 2-(2-hydrazinyl)-1,3-thiazole derivatives (V) [18], and compounds exhibiting potent antiproliferative activity (VI) [19] (Fig. 1).

Among the numerous thiazole-based pharmacophores, hydrazinyl thiazoles have emerged as promising candidates owing to their diverse biological activities and structural versatility. Hydrazinyl thiazole derivatives have demonstrated promising anticancer potential [20-22], encouraging the development of new analogues with improved biological profiles.

Various synthetic routes have been reported for their preparation including one-pot and multicomponent cyclocondensation reactions involving 1-indanone, thiosemicarbazide, and substituted phenacyl bromides. To improve the reaction efficiency, several catalytic systems have been explored, for example, xanthan gum-supported ionic liquids [23], graphite oxide [24], ZnO nanoparticles [25,26], Fe_3O_4@SiO_2-Pr-N=CH-$C_6H_4B(OH)_2$ [27] and MnO_2@Ag–S–CH_2–COOH nanocatalysts [28]. Despite these advances, many methods still require extended reaction times, elevated temperatures or catalyst-intensive conditions, highlighting the need for more efficient and sustainable synthetic protocols.

Among the various heterogeneous catalysts, titanium dioxide (TiO_2) has attracted considerable interest due to its low cost, chemical stability, non-toxicity, environmental com-

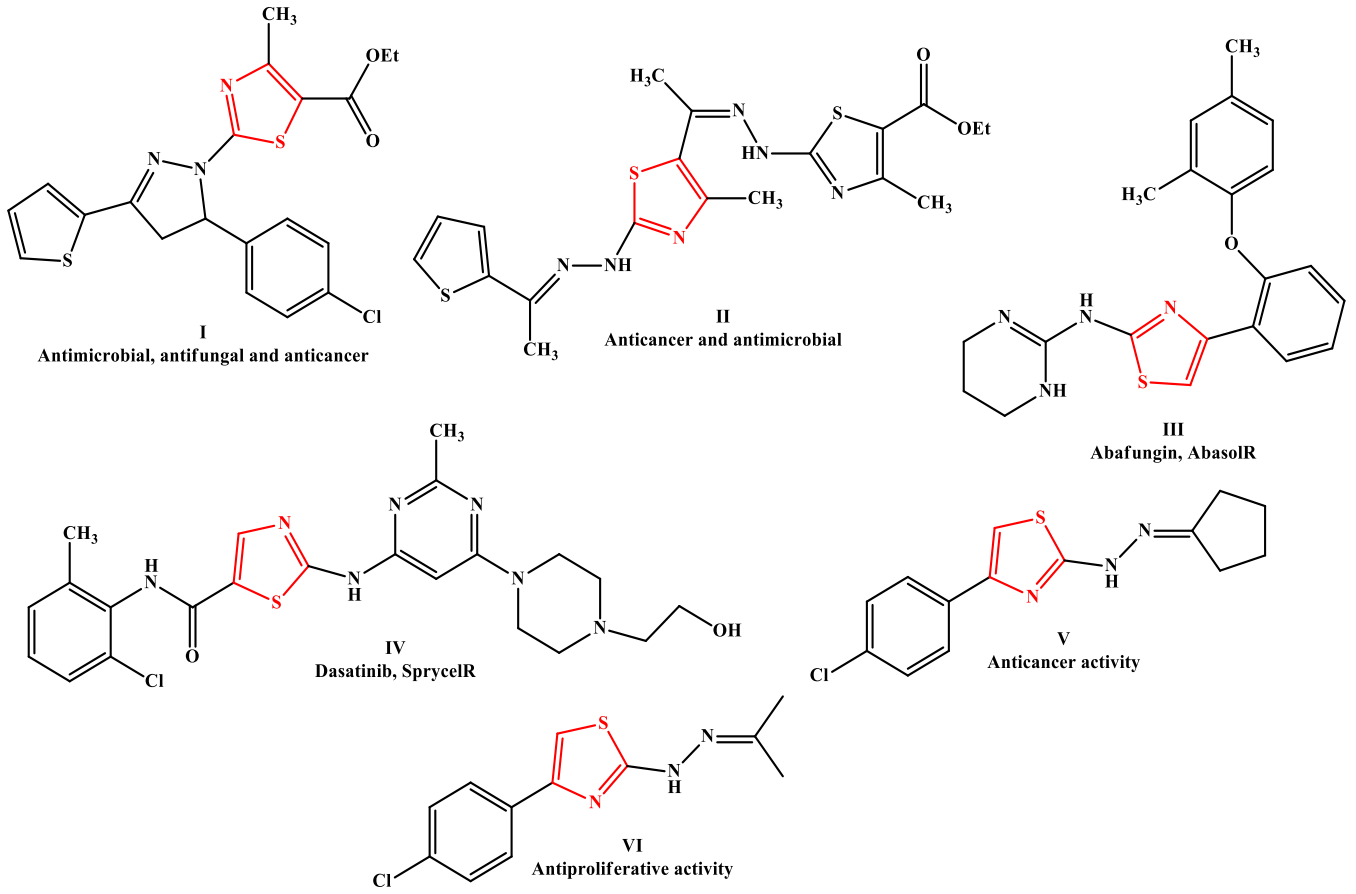


Fig. 1. Some biological active compounds of thiazoles

patibility, and ease of recovery. The surface of TiO_2 contains coordinatively unsaturated Ti^{4+} centers that can function as Lewis acidic sites, facilitating the activation of carbonyl groups and promoting subsequent condensation and cyclisation reactions. These characteristics make TiO_2 an attractive catalyst for multicomponent organic transformations [29]. In addition, its heterogeneous nature enables straightforward separation and reuse, thereby reducing waste generation and enhancing the sustainability of the synthetic process.

To investigate their therapeutic relevance, the synthesised compounds were evaluated against the MOC2 (mouse oral carcinoma 2) cell line [30,31], a widely used model of oral squamous cell carcinoma. This biological assessment was undertaken to establish preliminary anticancer activity, compare the relative efficacy of the synthesised derivatives and provide insight into structure–activity relationships.

EXPERIMENTAL

All reagents and solvents were of analytical grade and used without further purification. 1-Indanone, substituted phenacyl bromides and thiosemicarbazide were obtained from Sigma-Aldrich and/or TCI. Absolute ethanol was used as the reaction solvent, while chloroform, hexane and distilled water were employed during product isolation and purification.

Melting points were determined using open capillary tubes and are uncorrected. FTIR spectra were recorded on a Perkin-Elmer Spectrum Two spectrometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AVANCE III MHz spectrometer using DMSO-d_6 or $CDCl_3$ as solvents and tetramethylsilane (TMS) as the internal standard. Molecular masses and purity were confirmed using a Shimadzu LCMS-8040 high-resolution mass spectrometer.

Reaction optimisation: To identify the most efficient and sustainable reaction conditions, key parameters including solvent, catalyst loading, temperature and reaction time were systematically optimized. Among the solvents examined (water, ethanol, methanol and DMF), ethanol proved to be the most suitable due to its low toxicity, environmentally benign nature and ability to effectively dissolve both reactants and products. At temperatures below 60 ºC, the reaction proceeded slowly and resulted in lower product yields. Increasing the temperature above 80 ºC accelerated the reaction but led to partial decomposition of the products. At 70 ºC under reflux provided the best balance between reaction rate and product stability, allowing the reaction to reach completion within 20 min. Under these conditions, the desired hydrazinyl-thiazole derivatives (**4a-j**) were obtained in high yields and good purity, with only trace amounts of byproducts.

General synthesis of substituted hydrazinyl thiazole derivatives (4a-j): In a typical procedure, in a dry and clean 100 mL round bottom flask, a mixture of 1-indanone (1 mmol; 132 mg), thiosemicarbazide (1 mmol; 91 mg), (10% mmol TiO_2) and the corresponding substituted phenacyl bromide (1 mmol; 199 mg) were dissolved in 25 mL of absolute ethanol in a 100 mL round bottom flask. The reaction mixture was

refluxed at 70 ºC for 20-30 min. The progress of the reaction was monitored by thin-layer chromatography (TLC) (mobile phase used) using silica gel plates and an appropriate solvent system. After cooling to room temperature, the product was collected by vacuum filtration, washed with cold distilled water and purified by recrystallization from hot ethanol to afford analytically pure hydrazinyl thiazole derivatives (**4a-j**).

***N*-[4-(4-Chlorophenyl)thiazol-2-yl]-*N′*-indan-1-ylidene hydrazine (4a):** Yield: 78%; colour: light green, R_f: 0.5 (20% EtOAc/pet. ether); Elemental analysis of $C_{18}H_{14}ClN_3S$: calcd. (found) %: C, 63.98 (63.85); H, 4.17 (4.20); N, 12.44 (12.31); FTIR (KBr, ν_{max}, cm^{-1}): 3437.56 (N-H), 2697.28 (C-H), 1615.52 (C=N), 1581.92 (Ar-C=C), 1525.63, 1490.70 (arom. ring), 1439.24, 1408.71 (C-N), 1363.38, 1302.38 (C-N/C-S), 1207.83 (C-S, thiazole), 1083.05, 1008.16 (C-N), 869.70, 829.64 (Ar-C-H bend.), 765.54, 746.65, 718.69, 686.71 (substituted benzene), 614.84, 571.62 (C-S/ring def.); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.87 (s, 2H), 3.08 (s, 2H), 7.29 (s, 1H), 7.31 (s, 1H), 7.44 (s, 2H), 7.60 (s, 1H), 7.85 (d, 2H), 10.22 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 27.66, 28.28, 104.7, 120.8, 125.8, 127.1, 128.7, 130.2, 132.0, 133.5, 137.7, 148.9, 156.8 169.7; LCMS: *m/z* 338.8 $[M+H]^+$.

***N*-[4-(4-Fluorophenyl)thiazol-2-yl]-*N′*-indan-1-ylidene hydrazine (4b):** Yield: 70%; colour: brown, R_f: 0.5 (20% EtOAc/pet. ether); Elemental analysis of $C_{18}H_{14}FN_3S$: calcd. (found) %: C, 67.27 (67.10); H, 4.39 (4.41); N, 13.07 (12.95); FTIR (KBr, ν_{max}, cm^{-1}): 3063.19 (Ar-C-H), 1619.73 (C=N), 1599.32 (Ar-C=C), 1538.05, 1508.91 (arom. ring), 1467.93, 1442.99 (C-N), 1361.22 (C-N/C-S), 1240.54 (C-S, thiazole), 1167.85, 1071.80, 1023.93 (C-N), 887.03, 833.99, 808.24 (Ar-C-H bend.), 757.87, 745.92, 730.53, 692.36 (substituted benzene), 629.69, 609.72, 581.05, 561.85 (C-S/ring def.); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.86 (s, 2H), 3.07 (s, 2H), 7.21 (m, *J* = 7.6 Hz, 2H), 7.26 (m, *J* = 7.6 Hz 2H), 7.36 (d, 7.8 Hz, 2H), 7.60 (d, 8.4 Hz, 1H), 7.87 (d, 8.4 Hz, 2H), 10.97 (s,1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 27.5, 28.2, 103.5, 115.3, 120.8, 125.8, 127.0, 130.0, 131.2, 137.7, 147.9, 149.1, 156.5, 160.4, 169.6; LCMS: *m/z* 322.1 $[M+H]^+$.

***N*-Indan-1-ylidene-*N′*-[4-(4-nitrophenyl)thiazol-2-yl]-hydrazine (4c):** Yield: 75%; colour: bright orange, R_f: 0.5 (20% EtOAc/pet. ether); Elemental analysis of $C_{18}H_{14}N_4O_2S$: calcd. (found) %: C, 61.70 (61.55); H, 4.03 (4.07); N, 15.99 (15.80); FTIR (KBr, ν_{max}, cm^{-1}): 3335.67 (N-H), 3063.94 (Ar-C-H), 2629.15 (C-H), 1631.44 (C=N), 1600.90 (Ar-C=C), 1568.93, 1502.14 (arom. ring), 1465.63, 1441.64 (C-N), 1337.60 (C-N/C-S), 1207.08 (C-S, thiazole), 1106.40, 1057.34, 1024.06 (C-N), 903.59, 854.13, 794.72 (Ar-C-H bend.), 754.96, 730.91, 719.67 (substituted benzene), 624.03, 604.09, 579.81, 569.82, 558.96 (C-S/ring *def.*); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.88 (s, 2H), 3.07 (s, 2H), 7.30 (m, 1H), 7.35 (d, 2H), 7.60 (d, 1H), 7.62 (s, 1H), 8.10 (d, 2H), 8.28 (d, 2H) 10.22 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 27.5, 28.1, 108.6, 120.7, 124.1, 125.7, 127.0, 130.1, 137.6, 140.8, 146.1, 148.0, 156.6 169.9; LCMS: *m/z* 351.1 $[M+H]^+$.

***N*-Indan-1-ylidene-*N′*-[4-(4-methoxyphenyl)thiazol-2-yl]hydrazine (4d):** Yield: 73%; colour: cream, R_f = 0.5 (20% EtOAc/pet. ether); Elemental analysis of $C_{19}H_{17}N_3OS$: calcd. (found) %: C, 68.04 (67.90); H, 5.11 (5.15); N, 12.53 (12.40); FTIR (KBr, ν_{max}, cm^{-1}): 2546.72 (C-H), 1619.20 (C=N), 1584.76 (Ar-C=C), 1531.62, 1505.67 (arom. ring), 1461.42, 1441.59, 1406.27, 1360.62, 1293.62, 1251.38, 1182.60, 1072.27, 1021.83, 829.23, 749.51, 732.38, 691.28, 651.09, 630.27, 609.21, 583.40, 563.95; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.88 (s, 2H), 3.07 (s, 2H), 3.73 (m, 3H) 6.96 (m, 2H), 7.13 (m, 1H), 7.35 (s, 1H), 7.36 (s, 2H), 7.61 (s, 1H), 7.80 (m, 2H) 10.24 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 27.5, 28.2, 55.1, 101.7, 114.0, 120.7, 125.7, 126.9, 127.0, 130.0, 137.7, 148.0, 158.8, 169.3; LCMS: *m/z* 336.1 $[M+H]^+$.

***N*-Indan-1-ylidene-*N′*-[4-(4-trifluoromethylphenyl)-thiazol-2-yl]hydrazine (4e):** Yield: 73%; colour: light tan; R_f: 0.5 (20% EtOAc/pet. ether); Elemental analysis of $C_{19}H_{14}F_3N_3S$: calcd. (found) %: C, 61.11 (60.95); H, 3.78 (3.82); N, 11.25 (11.10); FTIR (KBr, ν_{max}, cm^{-1}): 3074.64 (Ar-C-H *str*.), 1616.38 (C=N *str*.), 1521.95, 1471.84 (arom. C=C *str*.), 1440.09, 1412.17 (C-H bend.), 1364.62, 1320.71 (C-N *str*.), 1172.99, 1136.64, 1095.24, 1068.21, 1012.27 (C-N/C-S *str*.), 842.22, 764.17, 745.51 (arom. C-H out-of-plane bend.); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.88 (s, 2H), 3.07 (s, 2H), 3.73 (m, 3H) 6.96 (m, 2H), 7.13 (m, 1H), 7.35 (s, 1H), 7.36 (s, 2H), 7.61 (s, 1H), 7.80 (m, 2H) 10.24 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 27.6, 28.2, 106.6, 120.7, 125.6, 126.1, 127.0, 130.1, 137.7, 138.4, 148.0, 148.8, 156.6 169.8; LCMS: *m/z* 374.1 $[M+H]^+$.

***N*-Indan-1-ylidene-*N′*-[4-(3-nitrophenyl)-thiazol-2-yl]-hydrazine (4f):** Yield: 85%; colour: pale yellow, R_f: 0.5 (20% EtOAc/pet. ether); Elemental analysis of $C_{18}H_{14}N_4O_2S$: calcd. (found) %: C, 61.70 (61.55); H, 4.03 (4.05); N, 15.99 (15.82); FTIR (KBr, ν_{max}, cm^{-1}): 3063.56 (Ar-C-H *str*.), 2628.33 (C-H *str*.), 1798.20, 1622.23 (C=N *str*.), 1600.06 (arom. C=C *str*.), 1524.09, 1466.84 (arom. ring), 1442.98 (C-H bend.), 1347.07 (C-N *str*.), 1240.83, 1208.07, 1167.41 (C-N/C-S *str*.), 1074.80, 1023.58 (C-N *str*.), 903.33, 864.56, 806.36 (arom. C-H bend.), 756.58, 738.74, 710.53 (substituted benzene); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.51 (s, 2H), 2.91 (s, 2H), 7.31 (m, 3H), 7.36 (m, 2H), 7.63 (m, 1H), 7.71 (d, 1H), 7.73 (d, 1H), 10.48 (s,1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 27.5, 28.2, 106.5, 120.0, 120.7, 122.0, 125.8, 127.0, 130.1, 131.5, 136.3, 137.6, 148.0, 156.5; LCMS: *m/z* 351.1 $[M+H]^+$.

***N*-[4-(3-Bromophenyl)-thiazol-2-yl]-*N′*-indan-1-ylidene hydrazine (4g):** Yield: 80%; colour: pale cream; R_f = 0.5 (20% EtOAc/pet. ether); Elemental analysis of $C_{18}H_{14}BrN_3S$: calcd. (found) %: C, 56.26 (56.10); H, 3.67 (3.70); N, 10.93 (10.80); FTIR (KBr, ν_{max}, cm^{-1}): 2926.31 (C-H *str*.), 2139.39 (weak overtone/combination band), 1619.73 (C=N *str*.), 1522.22, 1467.13 (arom. C=C *str*.), 1443.34 (C-H *bend*.), 1345.66 (C-N *str*.), 1288.42, 1194.99, 1151.59 (C-N/C-S *str*.), 1094.29, 1036.75 (C-N *str*.), 885.27, 751.83, 714.18, 681.66 (arom. C-H out-of-plane *bend*.); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.50 (s, 2H), 2.88 (s, 2H), 7.30 (m, 4H), 7.40 (d, 2H), 7.48 (d, 1H), 7.50 (d, 1H), 7.60 (d, 1H), 10.21 (s,1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 27.5, 28.2, 106.4, 120.7, 122.1, 124.4, 125.8, 127.0, 128.2, 130.1, 130.8, 136.8, 137.6 148.0, 156.37; LCMS: *m/z* 385.0 $[M+H]^+$, 387.0 $[M+2+H]^+$.

***N*-Indan-1-ylidene-*N′*-(4-*p*-tolyl-thiazol-2-yl)hydrazine (4h):** Yield: 80%; colour: light beige, R_f = 0.5 (20% EtOAc/ pet. ether); Elemental analysis of $C_{19}H_{17}N_3S$: calcd. (found) %:

C, 71.44 (71.25); H, 5.36 (5.40); N, 13.16 (13.00); FTIR (KBr, ν_{max}, cm^{-1}): 3439.29 (N-H *str*.), 2723.19 (C-H *str*.), 2153.61, 2009.27, 1989.13, 1963.38 (weak overtone/combination bands), 1683.91, 1614.75 (C=N *str*.), 1588.05 (arom. C=C *str*.), 1512.21, 1472.49 (arom. ring vibrations), 1440.39 (C-H *bend*.), 1364.66 (C-N *str*.), 1199.00, 1083.74 (C-N/C-S *str*.), 869.99, 817.12, 768.60, 747.40, 688.96 (arom. C-H out-of-plane *bend*.); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.32 (s,3H), 2.89 (s, 2H), 3.08 (s, 2H), 7.22 (d, 3H), 7.30 (d, 1H), 7.33 (s, 2H), 7.63 (s, 1H), 7.73 (s, 2H) 10.23 (s,1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm: 20.8, 27.6, 28.2, 103.1, 120.9, 125.6, 127.1, 129.3, 130.3, 137.3, 148.2, 157.2, 169.4; LC-MS: *m/z* 320.1 $[M+H]^+$.

***N*-Indan-1-ylidene-*N′*-[4-(4-methanesulfonyl-phenyl)-thiazol-2-yl]hydrazine (4i):** Yield: 75%; colour: pale yellow; R_f = 0.5 (20% EtOAc/pet. ether); Elemental analysis of $C_{19}H_{18}N_3O_2S_2$: calcd. (found) %: C, 59.36 (59.20); H, 4.72 (4.75); N, 10.93 (10.80); FTIR (KBr, ν_{max}, cm^{-1}): 3294 (N-H), 3019 (Ar-C-H), 2357 (CO_2), 2103, 2059 (overtones), 1636 (C=C), 1598, 1574 (Ar C=C), 1457, 1427, 1406 (C-H *bend*.), 1279, 1239, 1164, 1108, 1026 (C-N), 982, 902, 845, 808, 758, 722, 706, 668, 651, 581, 557, 523, 508 (arom. C-H *bend*.); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.50 (s, 2H), 2.89 (s, 2H), 3.11 (s, 3H), 7.30 (d, 1H), 7.33 (d, 2H), 7.36 (d, 2H), 7.61 (d, 2H), 8.12 (d, 2H) 11.22 (s,1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 27.5, 28.1, 43.6, 107.3, 120.7, 125.7, 126.0, 127.0, 130.0, 137.7, 139.1, 147.9, 148.9, 156.5 169.8; LCMS: *m/z* 385.1 $[M+H]^+$.

***N*-[4-(3-Fluorophenyl)thiazol-2-yl]-*N*'-indan-1-ylidene hydrazine (4h):** Yield: 72%; colour: light grey; R_f = 0.5 (20% EtOAc/pet. ether); Elemental analysis of $C_{18}H_{14}FN_3S$: C, 67.27 (67.10); H, 4.39 (4.42); N, 13.07 (12.95); IR (KBr, $cm^{-1)}$: FTIR (KBr, ν_{max}, cm^{-1}): 3345 (O–H), 2683 (C–H), 2182, 2125 (C≡N), 1950, 1896 (overtones), 1568, 1509 (Ar C=C/amide-II), 1468, 1417 (C–H *bend*.), 1367, 1319 (C–N), 1251, 1231, 1171, 1077, 1024 (C–O), 911, 871, 818, 773, 727, 672, 629, 599, 557, 525 (arom. C–H *bend*.); ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.87 (s, 2H), 3.08 (s, 2H), 7.02 (d, 1H), 7.11 (d, 1H), 7.30 (m, 2H), 7.37 (m, 2H), 7.50 (d, 2H), 7.71 (d, 1H) 10.44 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 27.6, 28.2, 105.3, 112.0, 114.1, 120.7, 121.6, 125.8, 127.0, 130.1, 130.7, 137.0, 148.0, 156.6, 161.3, 163.7, 169.6; LCMS: *m/z* 322.1 $[M+H]^+$.

Antiproliferative activity: MOC2 oral squamous cell carcinoma cells were cultured in complete IMDM/HAM′s F-12 medium supplemented with fetal bovine serum, hydrocortisone, epidermal growth factor, insulin and penicillin-streptomycin under standard conditions (37 ºC, 5% CO_2). Cells were seeded in 96-well plates at a density of 5×10^3 cells/well and allowed to attach overnight. The synthesized compounds **4a-f** were evaluated at concentrations ranging from 1.5625 to 100 μM for 48 h. Cell viability was determined using the MTT assay by incubating cells with MTT solution (0.5 mg/mL) for 3 h, followed by dissolution of the resulting formazan crystals in DMSO. Absorbance was measured at 570 nm using a microplate reader and IC_{50} values were calculated using GraphPad Prism software.

RESULTS AND DISCUSSION

The series of N-indan-1-ylidene-*N′*-(4-phenylthiazol-2-yl)-hydrazine derivatives (**4a-f**) were synthesized through a one-pot multicomponent reaction involving 1-indanone, thiosemicarbazide and substituted phenacyl bromides in the presence of TiO_2 as a catalyst and ethanol as the reaction medium. Refluxing the reaction mixture for 20-25 min afforded the desired products in high yields and purity (**Scheme-I**).

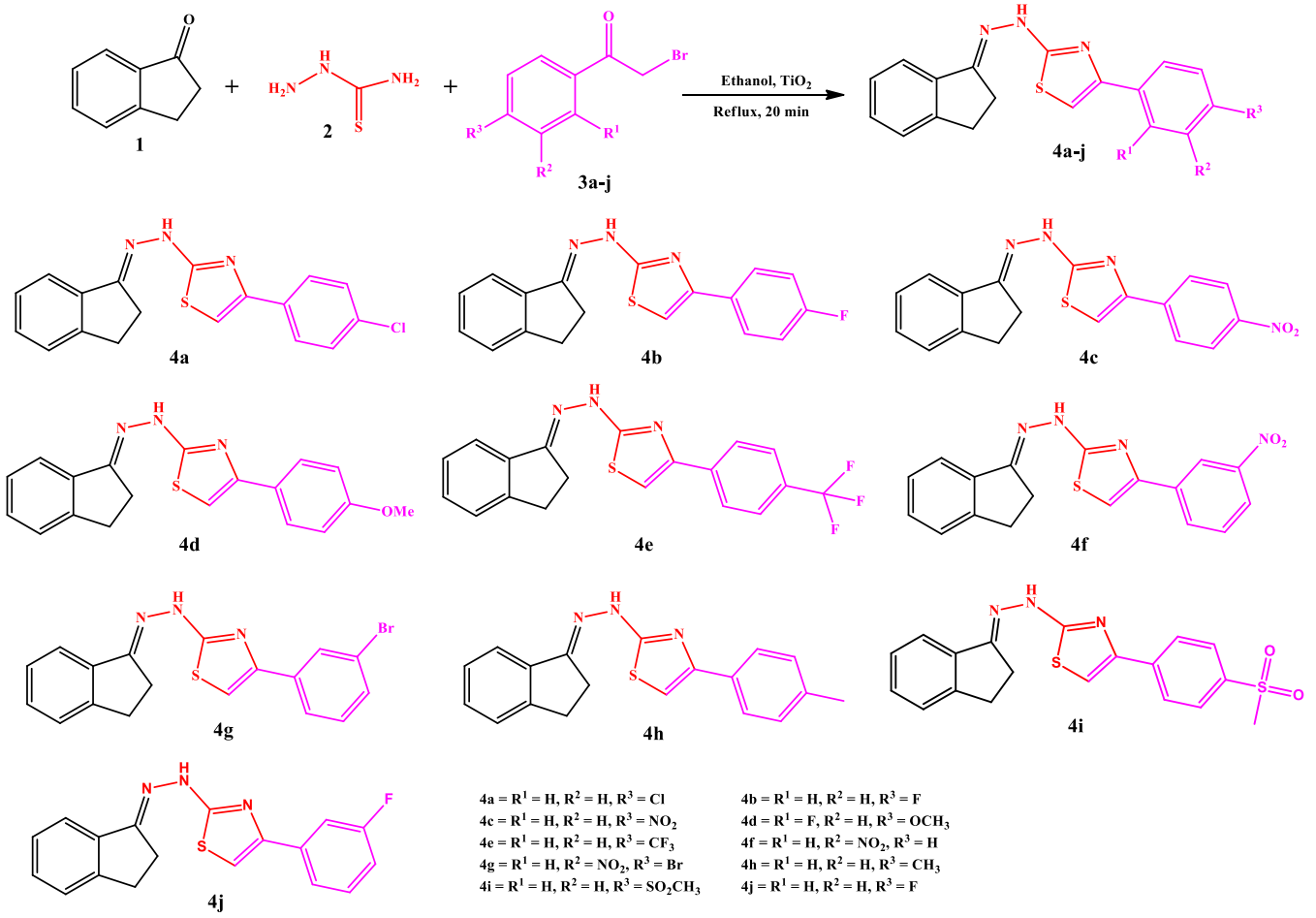
To establish the optimal reaction conditions, the effects of solvent, catalyst loading and temperature were systematically investigated using the synthesis of compound **4a** as a model reaction. Solvent screening revealed that ethanol provided the highest product yield among the solvents examined. Protic solvents such as water and methanol were less effective, whereas aprotic solvents including dichloromethane, DMF and acetonitrile afforded lower yields. The superior performance of ethanol may be attributed to its favourable solvation properties, environmental compatibility and ability to facilitate the cyclocondensation process.

The influence of catalyst loading was evaluated using different amounts of TiO_2. A catalyst loading of 10 mol% was found to be optimal, providing excellent product yields within a short reaction time. Increasing the catalyst amount beyond 10 mol% did not result in any significant improvement, while reactions conducted in the absence of TiO_2 exhibited distinctly lower conversion, highlighting the catalytic role of TiO_2 in promoting the transformation (Table-1).

Reaction temperature also played a crucial role in determining the efficiency of the process. The best results were obtained at 70 ºC, which enabled rapid conversion and high product yields (Table-1, entry 6). Lowering the temperature to 60 ºC reduced the reaction efficiency, whereas increasing it to 80 ºC produced no appreciable improvement in yield. Based on these findings, the optimized conditions were established as 10 mol% TiO_2 in ethanol under reflux at 70 ºC. Encouraged by these results, the optimized protocol was successfully extended to a range of substituted phenacyl bromides, affording the corresponding **4a-f** in excellent yields.

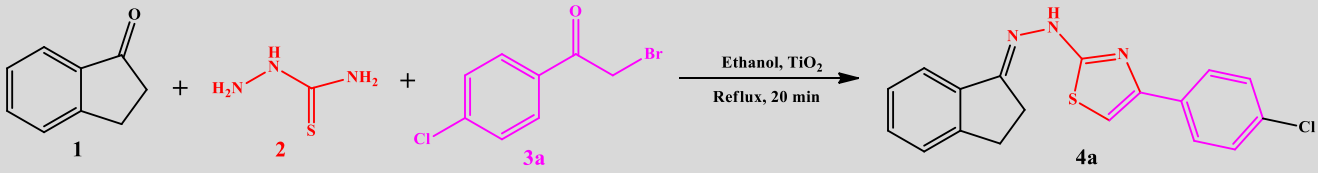
Mechanism: A plausible reaction mechanism for the formation of compound **4a** is outlined in **Scheme-II**. The process is proposed to begin with activation of the carbonyl group by the Lewis acidic Ti^{4+} sites on the TiO_2 surface, enhancing the electrophilicity of the carbonyl carbon. Subsequent nucleophilic attack by thiosemicarbazide generates an intermediate that undergoes dehydration to form the corresponding hydrazone. The sulphur atom then attacks the methylene carbon of the substituted phenacyl bromide, followed by elimination of HBr and intramolecular cyclization to generate the thiazole ring. A final dehydration step furnishes the target hydrazinyl-thiazole derivative. The high yield obtained under the optimized conditions highlights the effectiveness of TiO_2 as a reusable and environmentally benign Lewis acid catalyst for this transformation.

Antiproliferative activity: The antiproliferative potential of synthesised compounds **4a-j** was evaluated against MOC2 oral squamous carcinoma cells using the MTT assay following 48 h of treatment. The compounds exhibited varying degrees of growth inhibition, producing concentration-dependent red-



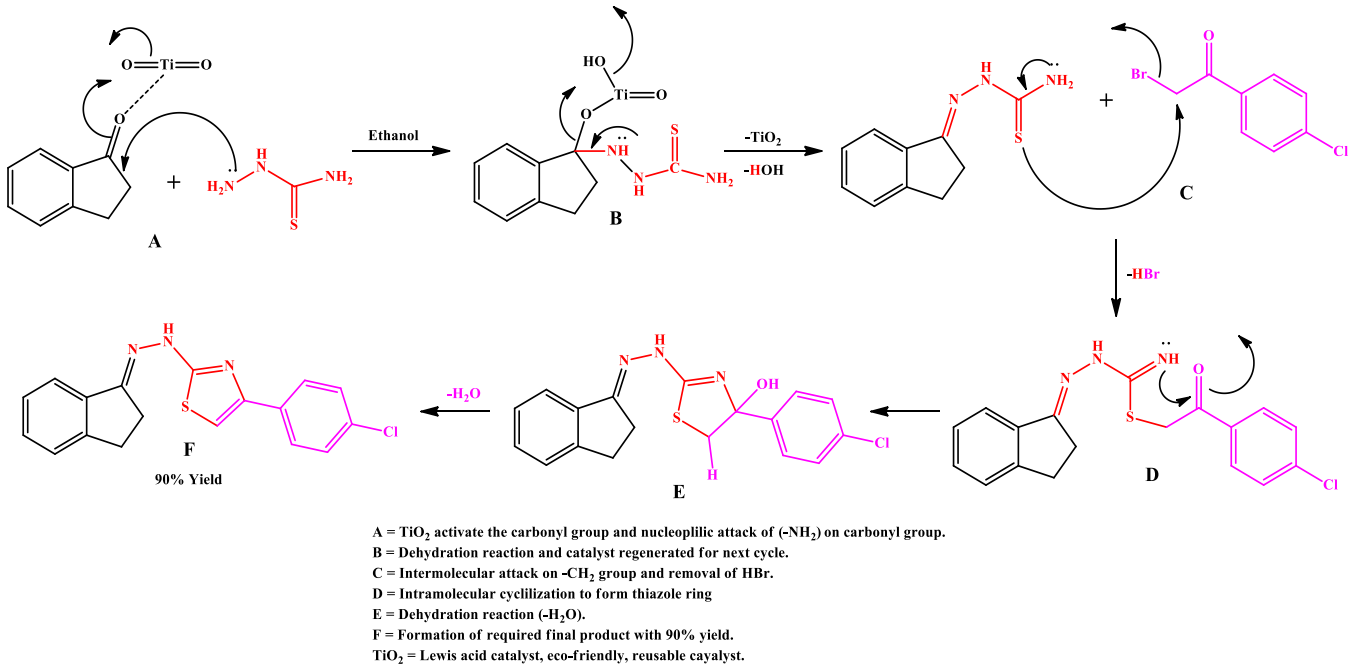
Scheme-I: Synthesis of hydrazinyl thiazole derivatives from 1-indanone (**1**), thiosemicarbazide (**2**) and 2-bromo-1-(4-chloro-phenyl)-ethanone (**4a-j**)

TABLE-1
SCREENING OF REACTION CONDITIONS WITH RESPECT TO TEMPERATURE, SOLVENT AND CATALYST LOADING[a]



Entry	Solvent	[a]Catalyst (TiO_2)	Temp. (°C)	Time (min)	[b]Yield (%)
1	Water	10 mol%	Rt	30	NR
2	Methanol	10 mol%	65	25	62
3	DMF	10 mol%	80	25	55
4	DCM	10 mol%	80	30	60
5	Acetonitrile	10 mol%	75	30	65
6	Ethanol	10 mol%	70	20	90
7	Ethanol	5 mol%	78	30	71
8	Ethanol	15 mol%	78	30	80
9	Ethanol	10 mol%	60	35	65
10	Ethanol	10 mol%	90	40	74
11	Ethanol	10 mol%	80	40	80
12	Ethanol	10 mol%	75	30	88
13	Ethanol	No catalyst	75	30	20

[a]Reaction condition: 1-indanone 1 mmol, thiosemicarbazide 1 mmol and 2-bromo-1-(4-chloro-phenyl)-ethanone 1 mmol, 10 mol% TiO_2 in ethanol, at 70 °C, [b]Isolated yields, Rt: Room Temperature, NR: No reaction.



Scheme-II: Plausible mechanism of the synthesis of N-[4-(4-chloro-phenyl)-thiazol-2-yl]-*N'*-indan-1-ylidene-hydrazine derivative (**4a**)

uctions in cell viability over the tested concentration range (1.5625-100 μM). The calculated IC_{50} values are summarized in Table-2. Among the studied derivatives, compound **4f** displayed the highest antiproliferative activity with an IC_{50} value of 26.53 μM, followed by compounds **4d** (30.48 μM) and **4h** (37.83 μM). Their ability to markedly decrease cell viability at higher concentrations shows the promising antiproliferative potential. Compound **4e** (53.88 μM) showed moderate activity, whereas **4b** (77.29 μM) exhibited a lower level of growth inhibition, as evidenced by its higher IC_{50} value.

TABLE-2
IC_{50} VALUES OF SYNTHESISED COMPOUNDS AGAINST MOC2 CELLS

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
4a	118.3	**4f**	26.53
4b	77.29	**4g**	134.0
4c	177.9	**4h**	37.83
4d	30.48	**4i**	315.6
4e	53.88	**4j**	177.7

However, compounds **4a**, **4c**, **4g**, **4i** and **4j** demonstrated relatively weak antiproliferative effects, with IC_{50} values ranging from 118.3 to 315.6 μM. Among these, compound **4i** was the least active derivative, exhibiting an IC_{50} value of 315.6 μM. The observed differences in biological activity suggest that structural modifications significantly influence the antiproliferative properties of this series.

Conclusion

In this result, an efficient titanium dioxide mediated methodology was established for the preparation of hydrazinyl thiazole derivatives using 1-indanone, phenacyl bromide and thiosemicarbazide as the fundamental building blocks. The reaction system operates under mild conditions and delivers the target compounds in good yields, demonstrated the practical applicability of TiO_2 as an environmentally benign catalyst. Comprehensive structural confirmation of the synthesised molecules was achieved through ^{1}H NMR, ^{13}C NMR, FTIR and mass spectroscopy analyses, verifying the successful construction of the hydrazinyl thiazole scaffold. Biological screening against MOC2 cell lines indicated that several derivatives process appreciable anticancer activity, emphasizing the biological relevance of this heterocyclic framework. Differences in cytotoxic response among the compounds further imply a dependence of anticancer activity on molecular structure. Collectively, the present study offers a robust synthetic strategy for hydrazinyl thiazole and highlights potential lead molecules for advanced anticancer research.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language. The authors reviewed and edited the content and take full responsibility for the published work.

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