# Green approach: Nanocrystalline titania-based sulfonic acid catalyst for the synthesis of piperazinyl-quinolinyl pyran derivatives

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## Abstract

A nanocrystalline titania-based sulfonic acid material was prepared, characterized and used as an effective, efficient and reusable catalyst for the synthesis of 2-amino-4-(2-(4-methylpiperazin-1-yl) quinolin-3-yl)-6-phenyl-4H-pyran-3-carbonitriles and 2-amino-4-(2-(4-methylpiperazin-1-yl)quinolin-3-yl)-6-(pyridin-4-yl)-4H-pyran-3-carbonitrile derivatives under solventfree conditions. This simple three component one-pot synthesis results in high yield products in 2 hours via conventional heating protocols. The catalyst was characterized by XRD, TEM, SEM, BET and Raman spectroscopy. The catalyst was recycled 5 times and recorded a decrease of 10 % in catalytic activity making it cost effective for large scale production. Copyright © 2016 VBRI Press.

Keywords: Sulfonic-acid catalyst, solvent-free, MCR, knoevenagel condensation.

#### Introduction

Heterocyclic compounds such as pyrans and pyranopyrans are important scaffolds since they amplify the bioactivity of compounds. These compounds exhibit a wide spectrum of pharmacological activities such as insecticidal [1], anti-viral [2], anti-tumor [3], inhibition of influenza virus [4] and phytotoxic activities [5]. Hence there has been a renewed interest in developing a general, versatile and more efficient method for the synthesis of pyrans and pyranopyran derivatives. A number of synthetic approaches to this class of compounds are documented [6] including the synthesis of 2-amino-4aryl-3-cyano-4H-pyrans by the cyclization of arylidene malononitrile and other active methylene compounds in the presence of organic bases such as piperidine [7], pyridine [8] and trimethylamine [9-10]. Most of these methods are unsuitable as they utilise volatile solvents and require long reaction time (~ 12 h) whilst catalyst recovery is also sometimes problematic. Recently, a onepot synthesis using Mg/La mixed oxide and MgO [11-12] as a basic catalyst as well as a multi-component synthesis of 2-amino-4H-pyran derivatives in aqueous medium [13-14] were reported. Most recently a new Brönsted acid, i.e., 4-(succinimido)-1-butane sulfonic acid (SBSA) was used for the synthesis of dihydropyrano [4, 3-b] pyran derivatives [15]. The recent years has witnessed gigantic advance in the catalysis of organic reactions by solid acid catalysts since they provide better opportunities for recovering and recycling from reaction mixtures. In particular, chemically bound adsorbed sulfonic acid on TiO<sub>2</sub> viz., TiO<sub>2</sub>-Pr-SO<sub>3</sub>H was synthesised, characterised then applied to the synthesis of quinoxalines [16], coumarins [17] and the promotion of the N-Boc protection of amines [18], however the scope of this catalyst is unlimited and needs further exploration. Green chemistry underlays twelve principles, and catalysis is one of the thumb principles which states using catalyst for a reaction instead of using a stoichiometric reagents which helps to increase selectivity, minimise waste and reduce reaction times and energy demands.

TiO<sub>2</sub>, the most widely studied and used in many applications because of its strong oxidizing abilities and for the decomposition of organic pollutants superhydrophilicity, chemical stability, long and durability, nontoxicity, low cost, and transparency to visible light. The photocatalytic properties of TiO<sub>2</sub> are due to the formation of photogenerated charge carriers (hole and electron) which are formed upon the absorption of ultraviolet (UV) light corresponding to the band gap. The photogenerated holes in the valence band diffuses TiO<sub>2</sub> surface and react with adsorbed water molecules, forming hydroxyl radicals (•OH). The photogenerated holes and the hydroxyl radicals oxidize organic molecules on the TiO<sub>2</sub> surface in vicinity. In the meantime, electrons in the conduction band typically participate in reduction processes, which typically reacts with molecular oxygen in the air to produce superoxide radical anions  $(O_{2*})$ . The development of new materials, however, is strongly required to provide enhanced performances with respect to the photocatalytic properties and to find new uses for TiO<sub>2</sub> photocatalysis. In this work, recent developments in the area of TiO<sub>2</sub>photocatalysis research, in terms of new materials from a structural design perspective, have been

carried out. The dimensionality associated with the structure of a  $TiO_2$  material can affect its properties and functions, including its photocatalytic performance [19].

In the current studies we report the excellent catalytic effect of TiO2–Pr–SO3H for the multi-component synthesis of 2-amino-4-(2-(4-methylpiperazin-1-yl) quinolin-3 yl)-6-phenyl-4H-pyran-3-carbonitriles and 2-amino-4-(2-(4-methylpiperazin-1-yl)quinolin-3-yl)-6- (pyridin-4-yl)-4H-pyran-3-carbonitrile derivatives using solvent-free conditions. In this strategy we decided to theoretically enhance the biological activity of the target molecule by using a new piperazinyl formyl quinoline derivative as a precursor for the multi-component synthesis, which confirms our greener approach to the work carried out.

## Experimental

#### General

Chemicals were purchased from Merck, Sigma Aldrich. The reaction monitoring and purity of the product was accomplished by TLC. FTIR spectra were recorded in the range of 4000-400cm<sup>-1</sup> on a JASCO FT/IR-460 spectrophotometer using KBr pellets. A Bruker D2 PHASER powder diffraction instrument; CuKa ray (wavelength  $\lambda = 0.154056$  nm), was used to measure in a continuous step-scan mode: the minimum width of the stage 0.031°, equilibrium time of 256 seconds, the operating voltage to 30 kV with 10 mA. Field-emission scanning electron microscopy (FESEM, Jeol JSM 7600F) was employed to characterise the morphology. High Resolution-Transmission Electron Spectroscopy (HR-TEM) was used. The BET gas sorption isotherms were measured at 77 K for N<sub>2</sub> and H<sub>2</sub>, and 273 and 298 K for CO<sub>2</sub> using Micromeritics Autopore 9500 system. Before recording gas sorption measurements, the sample was initially dehydrated at 423 K for 24 h under vacuum. Raman Spectroscopy was measured using the detector CCD (Triax) and the laser (He-Ne laser 632.8 nm). The NMR spectra were recorded in a Bruker Advance 400 MHz instrument. A TOF-MS analyser for accurate (HRMS) was used. The melting point (m.p) was recorded on a Buchi B-545 apparatus using open capillary tubes.

#### Catalyst preparation

#### Synthesis of 3-mercaptopropyltitania (MPT)

The synthesis of MPT was achieved by following ref. 18. Briefly, 10 g of  $TiO_2$  and 15 mL of (3-mercaptopropyl) trimethoxysilane were added to 30 mL dry toluene and the reaction mixture was refluxed for 24 h. After this period, the mixture was filtered, washed with acetone and dried.

#### Oxidation of 3-mercaptopropyltitania

MPT was oxidized as follows: an aliquot of 10 mL of 30 %  $H_2O_2$  and 30 mL methanol was added to MPT followed by two drops of conc.  $H_2SO_4$ . The reaction mixture was stirred for 24 h at room temperature, filtered and washed with distilled water and acetone to obtain solid acid catalyst TiO<sub>2</sub>-Pr-SO<sub>3</sub>H (**Scheme 1**).

#### General procedure for the synthesis of substituted 2-(4methylpiperazin-1-yl) quinoline-3-carbaldehyde (3)

The starting compound 2-chloro-3-formyl quinoline (CFO) (1) was prepared from acetanilide, DMF and POCl<sub>3</sub> by the Vilsmeir Haack reaction [19]. An aliquot (0.001 mol) of CFQ and potassium carbonate (0.002 mol) was added to a round bottom flask and an excess of 1methylpiperazine was added. The mixture was refluxed for 24 h at 200 °C; the reaction was monitored by TLC. After completion of the reaction, the reaction mass was cooled to room temperature and poured into water. It was then filtered, washed with water and dried. The crude product was purified by column chromatography using silica gel and a mobile phase of acetone and hexane (70:30) to produce a yellow powder of 90 % yield (m.p. 180 °C). IR (neat, cm<sup>-1</sup>): 2979, 2934, 2643, 2901, 2358, 2333, 1693, 1615, 1593, 1421, 1372, 1239, 952, 765, 512, 482 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  2.3 (s, CH<sub>3</sub>, 3H), 2.6 (t, CH<sub>2</sub>, 4H j=4.84 Hz), 3.47 (t, CH<sub>2</sub>, 4H, J=5.4Hz), 7.31(t, Ar, 1H, J =0.84Hz), 7.62 (t, Ar, 1H, J =1.44 Hz), 7.7 (d, Ar, 1H, J = 7.36 Hz), 7.76 (d, Ar, 1H, J = 8.48 Hz), 8.4 (brs, Ar, 1H), 10.09 (brs, 1H, CHO); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 45, 50, 54, 122, 123, 124, 127, 129, 132, , 142, 149, 158, 190. TOF MS ES+ Calcd mass 256.1450, Found: 256.1449 Anal. Calcd. For C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O: C, 70.56; H, 6.71; N, 16.46; Found: C, 70.58; H, 6.72; N, 16.43.

General procedure for the synthesis of 2-amino-4-(2-(4-methylpiperazin-1-yl) quinolin-3-yl)-6-phenyl-4Hpyran-3carbonitrile derivatives (6a-1)

To a mixture containing acetophenone derivative (5a-l) (1.0 mmol), 2-(4-methylpiperazin-1-yl) quinoline-3carbaldehyde (1.0 mmol) and malononitrile (1.0 mmol) was added TiO<sub>2</sub>-Pr-SO<sub>3</sub>H solid acid catalyst (0.07 g) and the resulting mixture was heated at 140 °C under solvent-free conditions. Upon completion of the reaction (monitored by TLC), 10 mL ethanol was added and the resulting mixture was filtered. The filter-cake was washed with warm ethanol (5 mL  $\times$  3) to effectively clean the catalyst. The filtrates were subsequently combined, the solvent evaporated *in vacuo* and the crude mixture was purified by column chromatography using silica gel and a mobile phase of acetone and hexane (70: 30). The recovered catalyst was dried and re-used in the subsequent runs.

General procedure for the synthesis of 2-amino-4-(2-(4methylpiperazin-1-yl) quinolin-3-yl)-6-(pyridin-4yl)-4Hpyran-3- carbonitrile derivatives (6m-n)

To a mixture of acetylpyridine derivatives (5m-n) (1.0 mmol), 2-(4-methylpiperazin-1-yl) quinoline-3carbaldehyde (1.0 mmol) and malononitrile (1.0 mmol) was added TiO<sub>2</sub>-Pr-SO<sub>3</sub>H solid acid catalyst (0.07 g) and the resulting mixture was heated at 140 °C under solvent-free conditions. Upon completion of the reaction (monitored by TLC), 10 mL ethanol was added and the resulting mixture was filtered. The filter-cake was washed with warm ethanol (5 mL  $\times$  3) to effectively clean the catalyst. The filtrates were subsequently combined, the solvent evaporated *in vacuo* and the crude mixture was purified by column chromatography using silica gel and a mobile phase of acetone and hexane (70: 30). The recovered catalyst was dried and re-used in the subsequent runs.

#### Spectroscopic information:

#### 2-amino-4-(2-(4-methylpiperazin-1-yl)quinolin-3-yl)-6phenyl-4H-pyran-3-carbonitrile (6a)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3413 (NH<sub>2</sub>), 3054(CH), 2989(CH), 2717, 2636, 2141, 2186 (C, 1654 (C=C), 1528, 1398, 1236, 767, 708. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  2.5 (s, 3H CH<sub>3</sub>), 2.8 (t, 4H, CH<sub>2</sub>), 3.27 (t, 4H, CH<sub>2</sub>), 6.99 (brs, 2H, NH<sub>2</sub>), 7.40(t, Ar,3H, J =7.52Hz), 7.52 (d, Ar,2H, J = 6 Hz), 7.60 (dd Ar,1H, J = 5.52 Hz), 7.67 (t, Ar,2H, J = 7.6 Hz), 7.72 (d, 2H CH, J = 8.24 Hz), 7.87 (d, Ar,2H, J = 7.92), 8.4 (brs, Ar,1H). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  30.62, 42.56, 45.6, 52.20, 91.97, 112.31, 116.82, 122.75, 124.24, 125.31, 126.36, 128.05, 128.48, 128.57, 129.34, 130.51, 137.30, 140.50, 146.05, 155.43, 155.64, 158.75, 161.65. TOF MS ES+ Calcd mass 423.21, Found: 424.3441 Anal. Calcd. For C<sub>26</sub>H<sub>26</sub>N<sub>5</sub>O: C 73.74, H 5.95, N 16.54; Found: C 73.76, H 5.97, N 16.58.

#### 2-amino-6-(2-hydroxyphenyl)-4-(2-(4-methylpiperazin-1yl) quinolin-3-yl)-4H-pyran-3-carbonitrile (6b)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3469, 3102, 3070, 2797, 2211, 1624, 1595, 1568, 1455, 1430, 1353, 1262, 1199, 1145, 1000, 759, 624. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  1.9 (s, 3H, CH<sub>3</sub>), 2.26 (t, 4H, CH<sub>2</sub>), 2.80 (t, 4H, CH<sub>2</sub>), 6.89 (dd, Ar,2H, J = 8.6 Hz), 6.96 (brs, 2H, NH<sub>2</sub>), 7.37(t, Ar,1H, J =0.92Hz), 7.47 (t, Ar,2H, J = 4.84 Hz), 7.65 (t, Ar,1H, J = 6.96 Hz), 7.72 (d, 2H, CH, J = 8.24 Hz), 7.87 (d, Ar,2H, J = 7.64 Hz), 8.38 (brs, Ar,1H), 9.93 (brs,1H,OH). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  42.66, 45.72, 52.26, 91.53, 111.99, 115.33, 115.69, 117.21, 122.87, 124.15, 124.25, 125.52, 126.35, 127.78, 128.03, 130.07, 130.41, 140.34,146.04, 130.51, 137.30, 140.50, 146.05, 155.23, 155.72, 158.59, 158.64, 161.86. For C<sub>26</sub>H<sub>25</sub>N<sub>5</sub>O<sub>2</sub>: C 71.05, H 5.73, N 15.93; Found: C 71.08, H 5.74, N 15.92.

#### 2-amino-6-(4-hydroxyphenyl)-4-(2-(4 methylpiperazin-1yl) quinolin-3-yl)-4H-pyran-3-carbonitrile (6c)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3426, 3043, 2765, 2194, 2153, 1614, 1591, 1560, 1529, 1514, 1457, 1405, 1361, 1282, 1251, 1166, 1018, 981, 834, 770. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  1.9 (s, 3H, CH<sub>3</sub>), 2.26 (t, 4H, CH<sub>2</sub>), 2.80 (t, 4H, CH<sub>2</sub>), 6.89 (d, Ar,2H, J = 8.6 Hz), 6.96 (brs, 2H, NH<sub>2</sub>), 7.37(t, Ar,1H, J =0.92Hz), 7.47 (d, Ar,2H, J = 4.84 Hz), 7.65 (t, Ar,1H, J = 6.96 Hz), 7.72 (d, 2H, CH, J = 8.24 Hz), 7.87 (d, Ar,2H, J = 7.64 Hz), 8.38 (brs, Ar,1H), 9.93 (brs,1H,OH). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  42.66, 45.72, 52.26, 91.53, 111.99, 115.33, 115.69,117.21, 122.87, 124.15, 124.25, 125.52, 126.35, 127.78, 128.03, 130.07, 130.41, 140.34,146.04, 130.51, 137.30, 140.50, 146.05, 155.23, 155.72, 158.59, 158.64, 161.86. Calcd. For C<sub>26</sub>H<sub>25</sub>N<sub>5</sub>O<sub>2</sub>: C 71.05, H 5.73, N 15.93; Found: C 71.08, H 5.76, N 15.92.

## 2-amino-4-(2-(4-methylpiperazin-1-yl)quinolin-3-yl)-6-(p-tolyl)-4H-pyran-3-carbonitrile (6d)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3450, 3419, 2999, 2719, 2636, 2472, 2198, 2182, 2144, 1610, 1596, 1566, 1524, 1436, 1406, 1236, 1208, 980, 821, 767.617. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  2.38 (s, 6H, 2CH<sub>3</sub>), 2.47 (t, 4H, CH<sub>2</sub>), 2.75 (t, 4H, CH<sub>2</sub>), 6.97 (brs, 2H, NH<sub>2</sub>), 7.33 (d, Ar,2H, J =7.96Hz), 7.35 (t, Ar,1H, J = 6.76 Hz), 7.52 (d, Ar,2H, J = 8.08 Hz), 7.64 (t, Ar,1H, J = 7.32 Hz), 7.72 (d, 2H, CH, J = 8.08 Hz), 7.88 (d, Ar,2H, J = 7.84 Hz), 8.4 (brs, Ar,1H). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  20.82, 40.04, 42.51, 45.60, 52.16, 91.70, 112.13, 113.67, 116.92, 124.17, 124.26, 125.38, 126.36, 128.06, 128.44, 128.70, 129.12, 129.45 130.47, 134.46, 139.02, 140.48, 146.06, 155.36, 155.63, 158.69, 161.73. Calcd. For C<sub>27</sub>H<sub>27</sub>N<sub>5</sub>O: C 74.12, H 6.22, N 16.01; Found C 74.13, H 6.24, N 16.04.

## 2-amino-4-(2-(4-methylpiperazin-1-yl) quinolin-3-yl)-6-(4 nitrophenyl)-4H-pyran-3-carbonitrile (6e)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 34941, 3127, 2849, 2713, 2204, 2185, 2148, 1713, 1616, 1598, 1530, 1406, 1345, 1289, 1206, 1015, 849, 774, 698. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  2.07 (s, 3H, CH<sub>3</sub>), 2.5 (t, 4H, CH<sub>2</sub>), 2.85 (t, 4H, CH<sub>2</sub>), 7.05 (brs, 2H, NH<sub>2</sub>), 7.38(d, Ar,2H, J =8.28Hz), 7.64 (t, Ar,1H, *J* =0.64 Hz), 7.73 (d, 2H, CH, J = 8.28 Hz), 7.88 (d, Ar,4H, J = 8.72 Hz), 8.37 (d, Ar,2H, J = 8.8 Hz), 8.41 (brs, Ar,1H). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  30.64, 40.61, 42.47, 45.65, 52.18, 91.23, 112.02, 116.41, 123.65, 124.25, 124.32, 125.10, 126.41, 128.09, 130.13, 130.62, 140.63, 143.81, 146.10, 147.85, 153.39, 155.63, 158.97, 161.58.Anal. Calcd. For C<sub>26</sub>H<sub>24</sub>N<sub>6</sub>O<sub>3</sub>: C 66.65, H 5.16, N 17.94; Found: C 66.63, H 5.18, N 17.96.

#### 2-amino-6-(4-fluorophenyl)-4-(2-(4-methylpiperazin-1-yl) quinolin-3-yl)-4H-pyran-3-carbonitrile (6f)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3529, 3390, 3057, 2996, 2715, 2628, 2481, 2204, 2187, 2155, 1616, 1528, 1438, 1238, 1161, 980, 835, 771, 570, 517. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>): δ 2.08 (s, 3H, CH<sub>3</sub>), 2.5 (t, 4H, CH<sub>2</sub>), 2.80 (t, 4H, CH<sub>2</sub>), 6.99 (brs, 2H, NH<sub>2</sub>), 7.38(d, Ar,4H, J =9.04Hz), 7.64 (t, Ar,2H, J =3.44 Hz), 7.73 (d, 2H, CH, J = 8.32 Hz), 7.84 (d, Ar,2H, J = 7.92 Hz), 8.4 (brs, Ar,1H). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>): δ 42.26, 42.83, 91.62, 112.18, 113.68, 115.41, 45.94, 52.36, 115.62,116.79, 122.58, 124.15, 124.24, 125.36, 126.38, 128.06, 130.45, 130.81, 130.89, 133.77, 140.43, 146.11, 154.25, 137.30, 155.80, 158.76, 161.45, 161.72. <sup>19</sup>F NMR (400 MHz, DMSOd<sub>6</sub>): δ -111.19. Calcd. For C<sub>26</sub>H<sub>24</sub>FN<sub>5</sub>O: C 70.73, H 5.48, N 15.86; Found: C 70.70, H 5.49, N 15.88.

#### 2-amino-6-(4-chlorophenyl)-4-(2-(4-methylpiperazin-1yl) quinolin-3-yl)-4H-pyran-3-carbonitrile (6g)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3373, 3246, 2939, 2746, 2358, 2204, 2185, 2152, 1595, 1618, 1526, 1409, 1491, 1240, 1090, 831, 758, 621, 556, 483. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  2.38 (s, 3H, CH<sub>3</sub>), 2.47 (t, 4H, CH<sub>2</sub>), 2.75 (t, 4H, CH<sub>2</sub>), 6.97 (brs, 2H, NH<sub>2</sub>), 7.33(d, 2H, J =7.96Hz), 7.35 (t, Ar,1H, *J* =6.76 Hz), 7.52 (d, Ar,2H,

J = 8.08 Hz), 7.64 (t, Ar,1H, J = 7.32 Hz), 7.72 (d, 2H, CH, J = 8.08 Hz), 7.88 (d, Ar,2H, J = 7.84 Hz), 8.4 (brs, Ar,1H). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  45.18, 48.21, 53.74, 69.73, 91.16, 111.89, 116.79, 122.45,123.96, 124.13, 124.39, 125.11, 125.82, 126.45, 126.64, 128.03, 128.63, 128.89, 130.16, 130.29, 130.43, 130.62, 131.55, 131.64, 134.09, 136.30, 139.76, 146.32, 153.43, 157.14, 157.47, 158.66, 162.04. Calcd. For C<sub>26</sub>H<sub>24</sub>ClN<sub>5</sub>O: C 68.19, H 5.28, N 15.29; Found C 68.21, H 5.30, N 15.27.

## 2-amino-6-(4-bromophenyl)-4-(2-(4-methylpiperazin-1yl) quinolin-3-yl)-4H-pyran-3-carbonitrile (6h)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3376, 2927, 2952, 2224, 2186, 2148, 1729, 1629, 1560, 1449, 1588, 1382, 1276, 1123, 778, 751, 572, 525. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  2.07 (s, 3H, CH<sub>3</sub>), 2.5 (t, 4H, CH<sub>2</sub>), 2.85 (t, 4H, CH<sub>2</sub>), 7.05 (brs, 2H, NH<sub>2</sub>), 7.38(d, Ar,2H, J =8.28Hz), 7.64 (t, Ar,1H, *J* =0.64 Hz), 7.73 (d, 2H, CH, J = 8.28 Hz), 7.88 (d, Ar,4H, J = 8.72 Hz), 8.37 (d, Ar,2H, J = 8.8 Hz), 8.41 (brs, Ar,1H). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  42.42, 43.41, 47.69, 52.55, 96.19, 107.54, 116.97, 122.23, 123.99, 124.55, 127.25, 131.14, 142.27, 146.18, 151.54, 157.55, 160.30. Calcd. For C<sub>26</sub>H<sub>24</sub>BrN<sub>5</sub>O: C 62.16, H 4.82, N 13.94; Found: C 62.19, H 4.81, N 13.96.

#### 2-amino-4-(2-(4-methylpiperazin-1-yl) quinolin-3-yl)-6-(thiophen-2-yl)-4H-pyran-3-carbonitrile (6i)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3460, 3424, 3105, 3063, 2982, 2710, 2637, 2479, 2207, 2185, 2143, 1613, 1596, 1527, 1397, 1245, 1215, 772, 718, 618. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  2.9 (s, 3H, CH<sub>3</sub>), 2.7 (t, 4H, CH<sub>2</sub>), 3.1 (t, 4H, CH<sub>2</sub>), 7.16 (brs, 2H, NH<sub>2</sub>), 7.26(t, Ar,1H, J = 3.96Hz), 7.4 (t, Ar,1H, J = 7.2 Hz), 7.68 (t, Ar,1H, J = 6.96 Hz), 7.74 (d, 2H, CH, J = 9.68 Hz), 7.82 (d, Ar,2H, J = 4.68 Hz), 7.9 (d, Ar,2H, J = 7.84 Hz), 8.4 (s, Ar,1H), <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  42.47, 45.65, 52.18, 91.23, 112.02, 116.45, 123.65, 124.32, 125.10, 126.41, 128.09,130.13, 130.62, 140.63, 143.81, 146.10, 147.85, 153.39, 158.97, 161.58. Calcd. For C<sub>24</sub>H<sub>23</sub>N<sub>5</sub>OS: C 67.11, H 5.40, N 16.30; Found: C 67.14, H 5.43, N 16.31.

## 2-amino-4-(2-(4-methylpiperazin-1-yl) quinolin-3-yl)-6-(naphthalen-1-yl)-4H-pyran-3-carbonitrile (6j)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3464, 3409, 3067, 2342, 2204, 2187, 2161, 1634, 1596, 1554, 1521, 1410, 1360, 1234, 1158, 1017, 786, 479. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  2.5 (s, 3H, CH<sub>3</sub>), 2.7 (t, 4H, CH<sub>2</sub>), 3.1 (t, 4H, CH<sub>2</sub>), 7.16 (brs, 2H, NH<sub>2</sub>), 7.26(t, Ar,1H, J =3.96Hz), 7.4 (t, Ar,1H, J =7.2 Hz), 7.68 (t, Ar,1H, J = 6.96 Hz), 7.74 (d, 2H, CH, J = 9.68 Hz), 7.82 (d, Ar,2H, J = 4.68 Hz), 7.9 (d, Ar,2H, J = 7.84 Hz), 8.1 (brs, Ar, 1H), 8.4 (brs, Ar, 1H), <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  42.47, 45.65, 52.18, 91.23, 112.02, 116.45, 123.65, 124.32, 125.10, 126.41, 128.09,130.13, 130.62, 140.63, 143.81, 146.10, 147.85, 153.39, 158.97, 161.58.Calcd. For C<sub>30</sub>H<sub>27</sub>N<sub>5</sub>O: C 76.09, H 5.75, N 14.79; Found: C 76.12, H 5.74, N 14.81.

#### 2-amino-6-(1-hydroxynaphthalen-2-yl)-4-(2-(4methylpiperazin-1-yl)quinolin-3-yl)-4H-pyran-3carbonitrile (6k)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3291, 3159, 2366, 2208, 1639, 1611, 1592, 1367, 1419, 1008, 1262, 1196, 951, 803, 748. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  2.0 (s, 3H CH<sub>3</sub>), 2.35 (t, 4H, CH<sub>2</sub>), 3.2 (t, 4H, CH<sub>2</sub>), 7.38(dd, Ar,2H, J =6.92Hz), 7.57 (brs, 2H, NH2), 7.65(d, 2H, CH, J =7.12Hz), 7.76 (t, Ar,2H, *J* =4.12 Hz), 7.96 (d, Ar,2H, J = 2.64 Hz), 8.08 (d, Ar,1H, J = 3.64 Hz), 8.24 (d, Ar,2H, j = 2.92Hz). 8.49 (d, Ar, 1H, J= 4.6Hz) 8.4 (brs, Ar, 1H), 10.22 (brs, 1H, OH). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  45.58, 48.71, 54.14, 112.45, 121.50, 123.05, 124, 126.49, 127.82, 128.24, 129.01, 135.02, 146.63, 148.05, 156, 157.54. Calcd. For C<sub>30</sub>H<sub>27</sub>N<sub>5</sub>O<sub>2</sub>: C 73.60, H 5.56, N 14.31; Found: C 73.62, H 5.58, N 14.32.

#### 2-amino-6-(anthracen-9-yl)-4-(2-(4-methylpiperazin-1-yl) quinolin-3-yl)-4H-pyran-3-carbonitrile (6l)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3456, 2857, 2727, 2506, 2223, 2185, 2150, 1654, 1589, 1561, 1493, 1458, 1281, 1215, 1129, 1060, 1025, 987, 786, 752, 609. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  2.07 (s, 3H, CH<sub>3</sub>), 2.73 (t, 4H, CH<sub>2</sub>), 3.1 (t, 4H, CH<sub>2</sub>), 7.03 (brs, 2H, NH<sub>2</sub>), 7.48(t, Ar,3H, J =0.76Hz), 7.74 (t, Ar,3H, J =5.84 Hz), 7.8 (d, Ar,4H, J = 8.24 Hz), 7.93 (d, Ar,4H, J = 7.84 Hz), 8.28 (brs, Ar, 2H). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  40.05, 42.81, 43.65, 45.63, 52.49, 80, 84.78, 116.53, 116.64, 122.39, 123.95, 124.74, 126.77, 128.12, 130.99, 140.47, 146.66, 155.74, 156.83, 158.86, 158.64, 162.96. Calcd. For C<sub>34</sub>H<sub>29</sub>N<sub>5</sub>O: C 77.99, H 5.58, N 13.37; Found: C 77.96, H 5.50, N 13.38.

## 2-amino-4-(2-(4-methylpiperazin-1-yl) quinolin-3-yl)-6-(pyridin-4yl)-4H-pyran-3-carbonitrile (6m)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3467, 3334, 2952, 2210, 2185, 2148, 1618, 1592, 1528, 1437, 1239, 1145, 760, 712,621. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  1.9 (s, 3H, CH<sub>3</sub>), 2.26 (t, 4H, CH<sub>2</sub>), 3.2 (t, 4H, CH<sub>2</sub>), 7.0 (brs, 2H, NH<sub>2</sub>), 7.38(t, Ar,1H, J =7.68Hz), 7.56 (t, Ar,1H, J =2.8 Hz), 7.65 (t, Ar,1H, J = 0.8 Hz), 7.72 (d, 2H, CH, J = 8.32 Hz), 7.8 (d, Ar,2H, J = 8.04 Hz), 8.0 (d,Ar,1H, J = 6.2 Hz), 8.32 (brs, Ar,1H), 8.68 (d, Ar,2H, J = 3.28Hz), 8.77 (brs, Ar,1H). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  45.16, 48.22, 53.80, 91.21, 112.01, 116.73, 122.29, 123.51, 123.95, 124.16, 125.79, 126.48, 128.06, 130.27, 133.42, 136.01, 139.83, 146.36, 148.47, 150.11, 151.39, 157.13, 158.81, 162.03. Calcd. For C<sub>26</sub>H<sub>24</sub>N<sub>6</sub>O<sub>3</sub>: C 66.65, H 5.16, N 17.94; Found: C 66.63, H 5.18, N 17.96.

#### 2-amino-4-(2-(4-methylpiperazin-1-yl) quinolin-3-yl)-6-(pyridin-4yl)-4H-pyran-3-carbonitrile (6n)

Yellow colour solid; IR (neat, cm<sup>-1</sup>): 3449, 3054, 2994, 2948, 2726, 2496, 2366, 2201, 2189, 2157, 1596, 1551, 1524, 1400, 1243, 981, 823, 770. <sup>1</sup>H NMR (400 MHz, DMSOd<sub>6</sub>):  $\delta$  1.9 (s, 3H, CH<sub>3</sub>), 2.26 (t, 4H, CH<sub>2</sub>), 2.42 (t, 4H, CH<sub>2</sub>), 7.06 (brs, 2H, NH<sub>2</sub>), 7.34(t, Ar,1H, J = 7.6Hz), 7.56 (d, 2H, *J* = 3.4 Hz), 7.76 (t, Ar,1H, J = 0.84 Hz), 7.72 (d, 2H, CH, J = 8.32 Hz), 7.87 (d, Ar,2H, J = 7.88 Hz),

8.3 (brs, Ar,1H), 8.72 (d, Ar,2H, J = 3.36Hz). <sup>13</sup>C NMR (100 MHz, DMSOd<sub>6</sub>):  $\delta$  40.7, 45.55, 48.62, 54.01, 90.49, 111.52, 116.42, 122.17, 122.92, 123.95, 124.13, 125.75, 126.49, 128.08,130.29, 139.73, 143.92, 145.11, 146.40, 149.93, 150.43, 152, 157.34, 158.85, 162.03, 172.08. TOF MS ES+ Calcd mass 424.20, Found: 424.31 Calcd. For C<sub>25</sub>H<sub>24</sub>N<sub>6</sub>O: C 70.73, H 5.70, N 19.80; Found: C 70.75, H 5.72, N 19.81.

## Molecular docking studies

Auto Dock 4.2 program which operate the Lamarckian Genetic Algorithm (LGA) was used to dock compound 6a&6n with the 3D structure of Hsp90. The crystal structure of Hsp90. (PDB id: 1AO6) was obtained from the Protein Data Bank and all water molecules were eliminated with successive addition of hydrogen atoms, followed by the computation of Gasteiger charges as required for LGA molecular docking procedure. The grid size along the x-, y-, z-axes and grid space were set to 60 Å, 60 Å and 60 Å and 0.403 Å for Hsp90. To include the whole subdomain IIA of Hsp90 during the docking process, the grid centre along the x-, y-, z-axes was set as 34.016 Å, 42.121 Å, and 50.644 Å for Hsp90. The Docking parameters were used, Genetic Algorithm (GA) population=150; maximum number of energy evaluations=250,000 and GA crossover mode of two points. For each docking simulation, 20 different conformers were generated and PyMOL package software was used for visualization of the interaction of docked protein-ligand complex. The conformation with the lowest binding free energy was used for further analysis.



Scheme 1. The reaction scheme for the synthesis of  $TiO_2$ -Pr-SO<sub>3</sub>H.

## **Results and discussion**

In the present study, we report a one-pot multicomponent synthesis of highly functionalised piperazinyl-quinolinyl pyran derivatives under solvent free conditions using nanocrystalline titania-based sulfonic acid catalyst. We selected the catalyst based on its new entry into the catalytic field and its efficacy based on minimal studies undertaken [16-17]. Briefly, the catalyst was synthesised in 2 stages: a mixture of TiO<sub>2</sub> and (3-mercaptopropyl) trimethoxysilane were refluxed for 24 h and after the work-up of the reaction, the product was oxidised with  $H_2O_2$  in an acidic medium (Scheme 1). The catalyst was characterised completely by several techniques.

The FT-IR spectra for pure  $TiO_2$  and  $TiO_2$ -Pr-SO<sub>3</sub>H revealed the following information: in the case of  $TiO_2$ , the absorption at 958, 1414, 2351 and 1645 cm<sup>-1</sup>

corresponds to the -OH stretching and bending vibrations of the adsorbed water. The spectrum of  $TiO_2$ -Pr-SO<sub>3</sub>H is similar to  $TiO_2$  however the absorption at 3243 cm<sup>-1</sup> is flattened which can be attributed to the modification of  $TiO_2$ . Also, the CH stretching vibrations of silylating agent was observed at 2954 cm<sup>-1</sup> and the absorption at 1211 cm<sup>-1</sup> is due to the Si-O stretching vibration. Furthermore, the absorptions at 1163 and 1141 cm<sup>-1</sup> is due to the stretching mode of S=O in SO<sub>3</sub>H.

The XRD patterns of  $TiO_2$  and  $TiO_2$ -Pr-SO<sub>3</sub>H (**Fig. 1**) clearly shows the anatase lines. It seems that the peak intensities of  $TiO_2$ -Pr-SO<sub>3</sub>H are almost the same as those of  $TiO_2$  thereby suggesting that the sulphate modification does not change the phase of  $TiO_2$ .



Fig. 1. Comparison of PXRD pattern of TiO<sub>2</sub> and TiO<sub>2</sub>-Pr-SO<sub>3</sub>H.

The representative SEM images of  $TiO_2$  (see **Fig. S1** in supporting information) Exhibit an aggregation of cloudlike structures of small spherical-shaped particles. The SEM micrographs of  $TiO_2$ -Pr-SO<sub>3</sub>H show some modifications with respect to  $TiO_2$  such that the primary surface structure of  $TiO_2$  has changed, however the cloud-like structure and small spherical-shaped particles still exists.



Fig. 2. The EDS pattern for  $TiO_2$  (image 1) and  $TiO_2$ -Pr-SO<sub>3</sub>H (image 2).

The EDS analysis for  $TiO_2$  and  $TiO_2$ -Pr-SO<sub>3</sub>H (**Fig. 2**) confirms the presence of all the elements and the actual weight % is presented in  $TiO_2$  element Ti, O, C, S,

weight % 35.95, 36.20, 17.24, 0, Atomic (%) 16.67, 50.25, 31.88, 0, The catalyst TiO<sub>2</sub>-Pr-SO<sub>3</sub>H element Ti, O, C, S, weight % 40.09, 43.22, 8.71, 0.30, Atomic (%) 19.21, 62, 16.64, 0.22, respectively.

Field-emission scanning electron microscopy was employed to characterise the morphology. The TEM image (see **Fig. S2** in supporting information) snapped at different place (a-1000 nm, b-200 nm, c-500 nm, d-100 nm, e-200 nm, and f-200 nm) shows the crystalline size of TiO<sub>2</sub>-Pr-SO<sub>3</sub>H which also has a mesoporous structure thereby suggesting a good surface for catalytic activity. The porous properties of TiO<sub>2</sub> and TiO<sub>2</sub>-Pr-SO<sub>3</sub>H, analysed by N<sub>2</sub> gas sorption measurements at 273K (see **Fig. S3** in supporting information) showed TiO<sub>2</sub> as a type-I adsorption isotherm which is characteristic of microporous material and the BET and Langmuir surface area of TiO<sub>2</sub> were calculated as 7 and 11 m<sup>2</sup>/g, respectively.

The  $N_2$  adsorption isotherm of TiO<sub>2</sub>-Pr-SO<sub>3</sub>H also indicated a type-I adsorption isotherm however the BET and Langmuir surface area were calculated as 16 and 37 m<sup>2</sup>/g, respectively.



Scheme 2. Synthesis of 2-amino-4-(2-(4-methylpiperazin-1-yl) quinolin-3-yl)-6-phenyl-4H-pyran-3-carbonitrile and 2-amino-4-(2-(4methylpiperazin-1-yl) quinolin-3-yl)-6-(pyridin-4yl)-4H-pyran-3carbonitrile derivatives.

Further investigation of the structure of TiO<sub>2</sub> and TiO<sub>2</sub>-Pr-SO<sub>3</sub>H were investigated by Raman spectroscopy (see Fig. S4 in supporting information) which showed absorption signals at 450, 470, 500, 570, 600, 2000, 3000, and 3650 cm<sup>-1</sup> for TiO<sub>2</sub>. The absorption signal of TiO<sub>2</sub>-Pr-SO<sub>3</sub>H showed absorptions signals at 470, 500, 650, 800, 900, 2000, 3000, 3650  $\text{cm}^{-1}$  with an additional signal at indicating the acidic functional group. In  $3450 \text{ cm}^{-1}$ order to synthesise some new biologically potent piperazinyl-quinolinyl pyran derivatives, a new starting compound viz., 2-(4-methylpiperazin-1-yl) quinoline-3carbaldehyde (3) was synthesised after using the Vilsmeir-Haack reaction to prepare 2- chloroquinoline-3carbaldehyde (1) from acetanilide [20]. Thereafter a and mixture of 1 1-methylpiperazine (2) was refluxed in a basic medium to

obtain 3 after 24 hours (compound 3). This compound was fully characterised by IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, TOF-MS and elemental analysis (**Fig. S5-6** in Supporting information).

In a preliminary study to synthesise 6a (Scheme 2) we compared a solvent-free system against ethanol and observed better yield in the latter case as reported in ref. 17. Hence to determine the optimum quantity of  $TiO_2$ -Pr-SO<sub>3</sub>H, the condensation of 3, malononitrile (4) and actophenone (5a), (Scheme 2) was carried out in the presence of different amount of catalyst (0.02, 0.05, 0.07 g) under solvent free conditions: 6a was produced and subsequently characterised by IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, TOF-MS and elemental analysis. It was found that increasing the quantity of the catalyst beyond 0.05 g did not increase the yield noticeably hence we selected this quantity as optimum for all subsequent reactions.

**Table 1.** A comparison of the reaction of a solvent/solvent-free system using TiO<sub>2</sub>-Pr-SO<sub>3</sub>H for the synthesis of 6a.

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield
1	TiO <sub>2</sub> - Pr- SO <sub>3</sub> H	EtOH	Reflux	6	60
2	TiO <sub>2</sub> - Pr- SO <sub>3</sub> H	MeOH	Reflux	6	50
3	TiO <sub>2</sub> - Pr- SO <sub>3</sub> H	CH <sub>3</sub> CN	Reflux	3	80
4	TiO <sub>2</sub> - Pr- SO <sub>3</sub> H	EtOH	Reflux	3	65
5	TiO <sub>2</sub> - Pr- SO <sub>3</sub> H	MeOH	Reflux	3	58
6	TiO <sub>2</sub> - Pr- SO <sub>3</sub> H	Neat	140	2	90

Whilst optimising the reaction conditions (**Table 1**), monitored by TLC, we observed that the use of a solvent needed a longer reaction time whilst the yield of 6a was lower. Herein we observed that if we conducted the solvent-free reaction at a higher temperature, viz., 140 °C some additional spots were observed on the TLC plate thereby suggesting formation of by-products. Also a shorter reaction time showed the presence of starting materials thereby indicating an incomplete reaction. The maximum yield of 6a (90%) was obtained under a solvent free condition after heating for 2 hours.



Fig. 3. The yield (%) of product (6a) versus the number of times the catalyst was re-used.

The re-usability potential of the catalyst TiO<sub>2</sub>-Pr-SO<sub>3</sub>H was also investigated in the model reaction to synthesise

6a: briefly, the solid was rinsed with acetonitrile and methanol and heated at 100 °C and taken for subsequent reactions. We found that the catalyst could be re-used five times without any significant loss of catalytic activity (Fig. 3) and concluded that it was sufficient and an important benefit which makes it useful if commercial application is required. The synthesis (Scheme 3 and 4) of piperazinyl-quinolinyl the functionalised pyran derivatives 6a-6n using monocrystalline titania-based sulfonic acid catalyst were undertaken in a solvent-free system for a reaction time of 2 hours at 140 °C.

Entry	Substrate (5a-n)	Produc	Tim	Yield	<b>M.p.</b> (° <b>C</b> )
		t (6a-n)	e (h)	(%)	_
1	C <sub>6</sub> H <sub>5</sub> COCH <sub>3</sub>	6a	2	90	260-262
2	HOC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	6b	2	85	280-283
3	HOC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	6c	2	90	285-287
4	CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	6d	3	78	278-280
5	O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	6e	2	75	275-278
6	FC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	6f	2	70	277-279
7	ClC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	6g	2	90	297-300
8	BrC <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	6h	2	87	290-292
9	C <sub>6</sub> H <sub>6</sub> OS	6i	3	83	280-283
10	C <sub>10</sub> H <sub>7</sub> COCH <sub>3</sub>	6j	2	90	288-290
11	HOC <sub>10</sub> H <sub>6</sub> COCH <sub>3</sub>	6k	2	90	285-287
12	$C_{16}H_{12}O$	61	2	75	267-269
13	C <sub>7</sub> H <sub>7</sub> NO	6m	2	88	270-272
14	C <sub>7</sub> H <sub>7</sub> NO	6n	2	90	285-287

The yield of the products (**Table 2**) ranged from 70 to 90 %. Compounds 6a-6n were characterised by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, MS-TOF whilst 6c, 6k and 6n included 90° DEPT and 135 °DEPT.



Scheme 2. Proposed mechanism for the synthesis of 2-amino-4-(2-(4-methylpiperazin-1-yl) quinolin-3-yl)-6-phenyl-4H-pyran-3-carbonitrile 6a at 140  $^{\circ}$ C.

Thus the one pot multi-component synthesis of the new piperazinyl-quinolinyl pyran derivatives using the less studied  $TiO_2$ -Pr-SO<sub>3</sub>H is a neat and efficient reaction which is selective for the formation of the sought after target. None of the above reaction has been documented hence a proposed mechanism is presented to support the formation of 6a which was the model reaction for the new

reaction scheme. In the first step, the acidic catalyst activates the aldehyde carbonyl functionality thereby enabling malononitrile to form a new covalent bond with loss of water as in the Knoevenagel condensation to produce 2-(2-(4-methylpiperazin-1-yl) quinolin-3-yl) methylene as an intermediate I. In the next step, the catalyst activates the nitrogen of intermediate I thereby facilitating a Michael addition to give intermediate II. This is followed by a simple intramolecular condensation reaction to produce intermediate III which subsequently undergoes a proton transfer reaction to produce 6a.

## Computational docking results

In order to support the experimental results, we performed computational docking analysis to create a model for Hsp90 (heat shock protein 90) –compound 6a & 6n complex. It has been stated earlier each domain of the SA proteins contains two sub domains (IA and B, IIA and B, IIIA and B) that possess common structural motifs. Sudlow site I and Sudlow site II (subdomains IIA and IIIA respectively) are the most probable binding sites of the ligands. Molecular docking analysis is performed using Auto dock 4.2 program and the energetically most feasible Hsp90-compound 6a & 6n complex is displayed in **Fig. 4 (a-b)**.



**Fig. 4.** (a) Molecular docking of the Hsp90-compound 6a and (b) Hsp90-compound 6n complex selected amino acid residues are represented by stick and cartoon models. Hydrogen bond is shown in pink dotted line.

Docking results clearly point out that compound 6a & 6n bind inside the binding pocket located in subdomain II A of Hsp90. It can be seen from Fig. 4 (a-b), compound 6a & 6n is located adjacent to the amino acid residues LEU-42, AGP-40, SER-36, LEU-89, ASN-91, ARG-32, LYS-98, ALA-213, PHE-120, SER-99, LYS-44, GLN-119, GLY-116, GLY-121 and THR101 of subdomain IIA of HSP90. Furthermore, carbonyl group containing O atom of compound 5m forms a hydrogen bond LYS-98 with bond length 1.9 Å. It is imperative to note from the computational observations that compound 6a & 6n is in the locality of TRP-214 amino acid residue of Hsp90. These obtained values just provide the probable geometry of the complexes; however the binding has been established experimentally. The ability of Hsp90 to clamp onto proteins allows to perform several functions including assisting folding, Hsp90 inhibited are investigated as anti-cancer drugs, preventing aggregation, and facilitating transport.

#### Conclusion

Thus the titanium based solid acid catalyst was used for the synthesis of highly functionalised piperazinylquinolinyl pyran derivatives either with a solvent or under solvent- free conditions in a relatively short reaction time but the catalytic activity is most effective in a solvent-free system. The preparation of the catalyst is simple, safe and highly re-usable. Furthermore this new one pot reaction creates a new type of piperazinyl-quinolinyl pyran derivatives which have suitable functionality for a host of possible biochemical applications.

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## **Supporting Information**



Fig. S1. The SEM image of  $\rm TiO_2$  (a, b and c) and  $\rm TiO_2\mathchar`-Pr-SO_3H$  (d, e and f).



Fig. S2. The TEM image of  $\rm TiO_2\mathchar`-Pr\mathchar`-SO_3H$  at different place (a, b, c, d, e, f).



Fig. S3. Adsorption and desorption isotherms of  $\rm TiO_2$  and  $\rm TiO_2\mbox{-}Pr\mbox{-}SO_3H$  at 273K.



**Fig. S4.** Raman shift of TiO<sub>2</sub> and TiO<sub>2</sub>-Pr-SO<sub>3</sub>H.



Fig. S5. The <sup>1</sup>H NMR of compound 3.

![](_page_8_Figure_14.jpeg)

Fig. S6. The <sup>13</sup>C NMR of compound 3.

![](_page_9_Figure_3.jpeg)

Fig. S7. The <sup>1</sup>H NMR of compound 6a.

![](_page_9_Figure_5.jpeg)

Fig. S8. The <sup>13</sup>C NMR of compound 6a.

![](_page_9_Figure_7.jpeg)

Fig. S9. The <sup>1</sup>H NMR of compound 6n.

![](_page_9_Figure_9.jpeg)

Fig. S10. The <sup>13</sup>C NMR of compound 6n.