Supporting Information:

A Simple and Efficient Synthesis of Cinepazide

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1. General procedure and experimental part of all compounds.
2. ^1H , Mass and IR spectrums of compounds all compounds.

Experimental section:

General methods: IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectro photometer using KBr optics. ^1H NMR spectra were recorded on Bruker-300 MHz, spectrometer in CDCl_3 using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectro meter operating at 70 eV.

(E)-Ethyl-3-(3,4,5-trimethoxyphenyl)acrylate (3): To a stirred solution of 3,4,5-tri methoxybenzaldehyde (1 gm, 5.1 mmol) in benzene was added ethyl-2-(tritylphosphinyli dene)-acetate (2.12 gm, 6.09 mmol) and the resulting reaction mixture was stirred at room temperature. Progress of the reaction was monitored by thin layer chromatography and the reaction was completed within 3 hours. Then the reaction mixture was adsorbed on silica gel (60-120 mesh) and eluted with ethyl acetate-hexane mixture (1:9). Pure compound was obtained as colorless liquid, 1.2 g (88.4%). IR (KBr): $\bar{\nu}$ 2974, 2939, 1703, 1633, 1583, 1505, 1455, 1416, 1340, 1314, 1278, 1243, 1182, 1152, 1122, 1036, 990, 823 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.35 (t, 3H, $J = 7.0$ Hz), 3.84 (s, 3H), 3.88 (s, 6H), 4.25 (q, 2H, $J = 7.0$ Hz), 6.29 (d, 1H, $J = 16$ Hz), 6.71 (s, 2H), 7.55 (d, 1H, $J = 16$ Hz); EIMS m/z (%): 289 (M^+Na , 10), 266 (10), 257 (100), 251 (45), 249 (15), 181 (15), 179 (60), 173 (30).

(E)-3-(3,4,5-Trimethoxyphenyl)acrylic acid (4): To a stirred solution of (E)-ethyl-3-(3,4,5-trimethoxyphenyl)-acrylate (1.2g, 4.5mmol) in THF-H₂O (12+6 mL) was added lithium hydroxide (0.16g, 6.75mmol) at 0 °C and continued stirring for 5 hours at room temperature. After completion of reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue was diluted by adding cooled water and neutralized with dilute hydrochloric acid. Then the reaction mixture was extracted with ethyl acetate (2x20 mL) and the combined organic layers was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) and eluted with ethyl acetate-hexane mixture (4:6 ratio). Pure compound was obtained as a white solid, 0.960 g (90%). Mp.125-126°C. ¹H NMR (CDCl₃+DMSO): δ 3.81 (s, 3H), 3.87 (s, 6H), 6.3 (d, 1H, *J* = 15.9 Hz), 6.75 (s, 2H), 7.50 (d, 1H, *J* = 15.9 Hz).; IR (KBr): $\bar{\nu}$ 3106, 3004, 2838, 2651, 1670, 1627, 1584, 1505, 1456, 1404, 1332, 1284, 1245, 1121, 994, 828, 729, 616 cm⁻¹.; EIMS *m/z* (%): 261 (M⁺Na, 100), 239 (80), 221 (98), 213 (10), 190 (10), 123 (15), 102 (20).

(E)-1-(Piperazin-1-yl)-3-(3,4,5-trimethoxyphenyl)-Prop-2-en-1-one (5): To a stirred solution of (E)-3-(3,4,5-trimethoxyphenyl)-acrylic acid (0.8g, 3.36 mmol) in dry DCM (5 mL) was added EDC (0.35g, 1.82 mmol) followed by HOBt (0.25g, 1.85 mmol) at room temperature. After 15 minutes stirring, the reaction mixture was cooled to 0°C and slowly added a mixture in which piperazine (0.29g, 3.37 mmol) was dissolved in dry DCM (5 mL) then added TEA (0.70 mL, 5.04 mmol). The resulting reaction mixture was stirred at room temperature for 5 hours. The completion of reaction was confirmed by TLC and the reaction mixture was diluted by adding DCM (10 mL) followed by saturated ammonium chloride solution (10 mL). The reaction mixture was extracted with DCM (2x10 mL) and the combined organic layer was washed with brine and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) and eluted with ethyl acetate-hexane mixture (3:7 ratio) to obtain a pure product as yellow syrup, 0.71 g (70%). IR (neat): $\bar{\nu}$ 3429, 2939, 2840, 1644, 1588, 1504, 1458, 1423, 1368, 1337, 1274, 1226, 1126, 1043, 1002, 827, 753, 660 cm⁻¹.; ¹H NMR (CDCl₃): δ 2.80-2.95 (m, 4H), 3.50-3.70 (m, 4H), 3.80 (s, 3H), 3.90 (s, 6H), 4.10-4.20 (brs, 1H), 6.60-6.75 (m, 3H), 7.55 (d, 1H, *J* = 15 Hz).; EIMS *m/z* (%): 329 (M+Na 20), 307 (100), 221 (75).

(E)-1-{4-[2-Oxo-2-(Pyrrolidin-1-yl)-ethyl]-piperazin-1-yl}-3-(3,4,5-trimethoxy phenyl)-prop-2-en-1-one

(1): To a stirred solution of (E)-1-(piperazin-1-yl)-3-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one (0.10g, 0.326mmol) in dry acetone (5mL) was added K_2CO_3 (0.09g, 0.652 mmol) and a catalytic amount of PTC (TBAI). After 30 minutes stirring was added 2-bromo-1-(pyrrolidin-1-yl)-ethanone (0.074g, 0.39 mmol), which was dissolved in dry acetone (5mL). The resulting reaction mixture was stirred for 3 hours at room temperature and the completion reaction was confirmed TLC, then solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (2x15 mL) and the combined organic layers was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a crude product, which was purified by column chromatography using silica gel (60-120 mesh) and eluted with ethyl acetate-hexane mixture (3:7) to obtain a pure product as yellow syrup, 0.124g (92%). IR (neat): 3058, 2925, 1954, 1760, 1701, 1593, 1551, 1515, 1489, 1464, 1442, 1393, 1354, 1252, 1179, 1158, 1077, 1025, 884, 819, 761, 697 cm^{-1} ; 1H NMR ($CDCl_3$): δ 1.80-2.01 (m, 4H), 2.50-2.70 (m, 4H), 3.13 (s, 2H), 3.35-3.50 (m, 4H), 3.65-3.80 (m, 4H), 3.82 (s, 6H), 3.90 (s, 3H), 6.50-6.75 (m, 3H), 7.52 (d, 1H, $J = 15$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 167.2, 165.3, 153.3, 142.9, 133.2, 122.4, 116.1, 105.3, 104.9, 60.9, 56.2, 56.0, 52.7, 46.1, 45.8, 40.8, 26.1, 24.0.; EIMS m/z (%): 440 (M^+Na , 60), 418 (50), 242 (100), 139 (8).

¹H-NMR spectrum of compound (3)

EIMS spectrum of compound (3)

IR spectrum of compound (3)

¹H-NMR spectrum of compound (4)

EIMS spectrum of compound (4)

IR spectrum of compound (4)

¹H-NMR spectrum of compound (5)

EIMS spectrum of compound (5)

IR spectrum of compound (5)

¹H-NMR spectrum of compound (1)

EIMS spectrum of compound (1)

IR spectrum of compound (1)

IR Spectrum of (E)-1-(4-(2-oxo-2-(pyrrolidin-1-yl)ethyl)piperazin-1-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

Bench: Thermo Nicolet
Resolution: 4 cm⁻¹

¹³C-NMR spectrum of compound (1)