Supporting Information

Utilization of Transition Metal Fluoride Based Solid Support Catalysts for the Synthesis

of Sulfonamides: Carbonic Anhydrase Inhibitory Activity and *in Silico* Study

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Experimental

General Information

Iron fluoride, Molecular sieve 4Å, p-toluenesulfonyl chloride (99%), different aromatic amines, cyclohexane ($\geq 99.5\%$), phenyl hydrazine derivatives, trimethylsilyl azide (99%), dimedone (95%), aromatic aldehydes, ammonium acetate etc. were purchased from Sigma Aldrich and used without any purification unless otherwise stated. The progress of reactions was monitored using thin layer chromatography (TLC) on silica gel 60 aluminium-backed plates 0.063-0.200 mm. Analytical grade solvents such as, ethanol, ethyl acetate, n-hexane were used. For TLC plate visualization, UV irradiation at 254 nm was used. The TLC staining reagents, KMnO₄ or vanillin were also used (where required) for visualization of TLC plates. Infrared (IR) spectra were recorded on Bruker Vector-22 spectrometer. The Bruker spectrometers of 300 MHz, 400 MHz, or 500 MHz were used for ¹H and ¹³C NMR spectroscopic data. The chemical shifts were recorded on the δ -scale (ppm) using residual solvents as an internal standard (DMSO; ¹H 2.50, ¹³C 39.43 and CHCl₃; ¹H 7.26, ¹³C 77.16). Coupling constants were calculated in Hertz (Hz) and multiplicities were labelled s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet) and the prefixes br (broad) or app (apparent) were used. Mass spectra (EI⁺ and FAB) were recorded on Finnigan MAT-321A, Germany. Melting points of solids were determined using a Stuart[™] melting point SMP3 apparatus.



Figure-S1: (a) size and morphology of molecular sieves (b) Particle size distribution respectively.

b

а



Scheme-S1: Fisher indole synthesis 6a-6h of different substituted indoles by using solid supported catalyst (FeF₃/MS 4Å). *Note*: Reactions have been carried out by solid supported catalyst (wt% 1/1, 100 mg) in ethanol

General procedure for the synthesis of indole derivatives

An oven dried flask was charged with FeF₃ supported crushed molecular sieves 4Å (100 mg), and ethanol (5 mL). To the reaction flask, subsequently, the substituted phenyl hydrazine hydrochloride (1 mmol, 1 equiv.), cyclohaxanone (1 mmol, 1 equiv.) was added at room temperature and mixture was heated at reflux (78-80 °C) for 1 h until the completion of reaction as monitored via TLC (ethyl acetate : hexane = 1:9). The crude product was purified with gradient eluents EtOAc/Hexane (1:9 to 1:1) to get the corresponding pure products (6a-d) in different yields.

2,3,4,9-Tetrahydro-1*H*-carbazole (6a)

Slightly yellow color, yield 70 %, 119 mg, M.P. 116-118 °C, (Lit. 117.4-118.9 °C) ^[1], IR v_{max} , cm⁻¹: (Solid, KBr) 3398 (NH), 1655 C=C, 1585, 1446, 1233 . ¹H-NMR (400 MHz, DMSOd₆): δ_{H} 10.58 (1H, brs, N*H*), 7.30 (1H, d, Ar*H*, *J*= 8.0 Hz), 7.21 (1H, d, Ar*H*, *J*= 8.0 Hz), 6.95 (1H, t, Ar*H*, *J*= 8.0 Hz), 6.90 (1H, t, Ar*H*, *J*= 8.0 Hz), 2.67 (2H, app t, CH₂ = 6.0 Hz), 2.60 (2H, app t, CH₂, *J* = 6.0 Hz), 1.81-1.79 (4H, m, 2CH₂). ESI-MS, *m/z* (M⁺1) 172.1.

6-Methyl-2,3,4,9-tetrahydro-1*H*-carbazole (6b)

Slightly yellow color, Yield 67%, 124 mg, M.P. 141-143 °C, (Lit. 142-144 °C) ^[2, 3] IR v_{max} , cm⁻¹: (Solid, KBr) 3394 (NH), 3021, 1651 C=C, 1589, 1468, 1195. ¹H-NMR (400 MHz, DMSO- d_6): δ_{H} 10.42 (1H, brs, N*H*), 7.10 (2H, app d, Ar*H*, *J*= 8.0 Hz), 6.78 (1H, d, Ar*H*, *J*= 12.0 Hz), 2.67 (2H, app t, C H_2 , *J*= 4.0 Hz), 2.58 (2H, app t, C H_2 , *J*= 4.0 Hz), 2.33 (3H, s, C H_3), 1.81-1.75 (4H, m, 2C H_2). ESI-MS, *m/z* (M⁺1) 186.13.

6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazole (6c)

Yellow color, Yield 73%, 138 mg, M.P. 94-96 °C, (Lit. 94-95 °C) ^[4]., IR v_{max} , cm⁻¹: (Solid, KBr) 3406 (NH), 1626, 1583, 1480,1230. ¹H-NMR (400 MHz, DMSO- d_6): δ_H 10.69 (1H, brs, N*H*), 7.20 (1H, dd, Ar*H*, J = 8.0, 4.0 Hz), 7.05 (1H, d, Ar*H*, J = 8.0 Hz), 6.80 (1H, app td, Ar*H*, J = 8.0, 4.0 Hz), 2.67 (2H, app t, C H_2 , J = 4.0 Hz), 2.56 (2H, app t, C H_2 , J = 4.0 Hz), 1.78 (4H, m, 2C H_2). ESI-MS, m/z (M⁺1) 190.1.

6-Bromo-2,3,4,9-tetrahydro-1*H*-carbazole (6d)

Pale yellow color, Yield 63%, 156 mg, M.P. 152-154 °C, (Lit. 152.6-154.1 °C) ^[5]., IR v_{max} , cm⁻¹: (Solid, KBr) 3404 (NH), 1617, 1577, 1465. ¹H-NMR (400 MHz, DMSO- d_6): δ_{H} 10.84 (1H, brs, N*H*), 7.46 (1H, s, Ar*H*), 7.19 (1H, d, Ar*H*, J = 8.0 Hz), 7.07 (1H, d, Ar*H*, J = 8.0 Hz), 2.67 (2H, app brs, C H_2), 2.56 (2H, app brs, C H_2), 1.78 (4H, app brs, 2C H_2) ^[5]. ESI-MS, m/z (M + H) 250.

6-Methoxy-2,3,4,9-tetrahydro-1*H*-carbazole (6e)

Pale yellow color, Yield 69%, 138 mg, M.P. 107-109 °C, (Lit. 106-108 °C) ^[2]. IR v_{max} , cm⁻¹): (Solid, KBr) 3389 (NH), 1624, 1591, 1484, 1219. ¹H-NMR (400 MHz, DMSO- d_6): δ_H 10.39 (1H, brs, N*H*), 7.10 (1H, d, Ar*H*, J = 8.0 Hz), 6.80 (1H, d, Ar*H*, J = 4.0 Hz), 7.19 (1H, dd, Ar*H*, J = 8.4, 4.0 Hz), 3.72 (3H, s, CH₃-O), 2.65 (2H, app t, CH₂, J = 4.0 Hz), 2.56 (2H, app t, CH₂, J = 4.0 Hz), 1.81-1.75 (4H, m, 2CH₂) ^[2]. ESI-MS, m/z (M + H) 202.1.

6-Chloro-2,3,4,9-tetrahydro-1*H*-carbazole (6f)

Off-white colour, Yield 59%, 121 mg, M.P. 161-163 °C, (Lit. 162-163 °C) ^[2], IR v_{max} , cm⁻¹: (Solid, KBr) 3404 (NH), 1578, 1468, 1231. ¹H-NMR (400 MHz, DMSO-*d*₆): δ_{H} 10.82 (1H, brs, N*H*), 7.33 (1H, d, Ar*H*, *J* = 3.0 Hz), 7.23 (1H, d, Ar*H*, *J* = 8.0 Hz), 6.94 (1H, dd, Ar*H*, *J* = 12.0, 4.0 Hz), 2.68 (2H, app t, Ar*H*, *J* = 8.0 Hz), 2.56 (2H, app t, C*H*₂, *J* = 8.0 Hz), 1.82-1.75 (4H, m, 2C*H*₂), 1.82 (4H, m, 2C*H*₂). ESI-MS, *m/z* (M + H) 206.1

5-Nitro-2,3,4,9-tetrahydro-1*H*-carbazole (6g)

Orange color, Yield 30%, 78 mg, M.P. 150-152 °C, (Lit. 152 °C) ^[6], IR v_{max} , cm⁻¹: (Solid, KBr) 3351 (NH), 1672, 1567, 1468, 1271. ¹H-NMR (400 MHz, DMSO- d_6): δ_H 11.60 (1H, brs, N*H*), 7.72 (1H, d, Ar*H*, J= 8.0 Hz), 7.66 (1H, d, Ar*H*, J= 12.0 Hz), 7.15 (1H, t, Ar*H*, J= 10.0 Hz), 2.80-2.73 (4H, m, 2C H_2), 1.82-1.74 (4H, m, 2C H_2). ESI-MS, m/z (M + H) 217.1.

7-Nitro-2,3,4,9-tetrahydro-1*H*-carbazole (6h)

Orange color, Yield 11%, 28 mg, M.P. 168-170 °C, (Lit. 169 °C) ^[6], IR v_{max} , cm⁻¹: (Solid, KBr) 3392 (NH), 1650, 1547, 1462, 1221. ¹H-NMR (400 MHz, DMSO- d_6): δ_H 11.52 (1H, brs, N*H*), 8.17 (1H, d, Ar*H*, J = 2.8 Hz), 7.85-7.82 (1H, dd, Ar*H*, J = 12.0, 4.0 Hz), 7.50 (1H, d, Ar*H*, J = 12.0 Hz), 2.78 (2H, app t, C H_2 , J = 8.0 Hz), 2.56 (2H, app t, C H_2 , J = 8.0 Hz), 1.83-1.80 (4H, m, 2C H_2). ESI-MS, m/z (M + H) 217.1.



Scheme-S2: Synthesis of substituted 1H-tetrazoles.

2.3. Synthetic protocol for the synthesis 1H-Tetrazoles

In a typical procedure, the corresponding benzonitriles (1 mmol) were added with trimethylsilyl azide (3 mmol) to an over dried reaction flask. 100 mg of prepared catalyst was taken in reaction flask and rubber septum was capped tightly. The reaction mixture was heated at 115-125 °C for formation of desired product in a reflux assembly, reaction was monitored via TLC and was continued until complete disappearance of starting materials. The catalyst was separated by filtration while the mixture was still hot. The filtrate was allowed to cool down at ambient temperature. Ethyl acetate (15 mL) was used to dilute the filtrate and washed with 1N hydrochloride (20 mL) in a separating assembly. The organic layer was dried over anhydrous NaSO₄, followed by filtration. This filtrate was concentrated under reduced pressure to get the final product as a solid.

5-(4-Fluorophenyl)-1*H*-tetrazole (8a)

Off-white colour, Yield 71%, 116 mg, 184-186 °C, (Lit. 185 °C) ^[7, 8], IR v_{max} , cm⁻¹: (Solid, KBr), 3663, 3416, 1664 C=N stretch, 1550 N=N stretch, 1164, 1121. ¹H-NMR (400 MHz, DMSO- d_6): $\delta_{\rm H}$ 8.09 (2H, app dd, Ar*H*, *J* = 8.0, 4.0 Hz), 7.83 (2H, app t, Ar*H*, *J* = 8.0 Hz). EI-MS, m/z (%), 164.1 (62), 136 (100), 121 (33), 109 (87), 95 (17).

5-(4-Bromophenyl)-1*H*-tetrazole (8b)

Pale yellow colour, Yield 69%, 156 mg, M.P. 256-260 °C, (Lit. 257-258 °C) ^[9] ^[10], IR v_{max} , cm⁻¹: (Solid, KBr), 3663, 3414, 1660 C=N stretch, 1563 N=N stretch, 1157. ¹H NMR (400 MHz, DMSO- d_6): δ_{H} 7.98 (2H, d, Ar*H*, J = 8.0 Hz), 7.83 (2H, d, Ar*H*, J = 8.0 Hz). EI-MS, m/z (%), 224 (23), 198 (100), 90(38), 75 (10).

5-(4-Methoxyphenyl)-1*H*-tetrazole (9c)

Rust colour, Yield 70 %, 123 mg, M.P. 226-228 °C, (Lit. 227 °C) ^[9], IR v_{max} , cm⁻¹: (Solid, KBr), 3700, 3662, 3636, 3576, 3413, 1664 C=N stretch, 1550 N=N stretch, 1163. ¹H-NMR (400 MHz, DMSO-*d*₆): $\delta_{\rm H}$ 7.98 (2H, d, Ar*H*, *J* = 8.8 Hz) 7.16 (2H, d, Ar*H*, *J* = 8.8 Hz), 3.84 (3H, s, OC*H*₃). FABP-MS, M⁺¹ (%), 177.0 (72).



Scheme-S3: Synthesized of substituted phenyl 1,4-dihydropyridines.

2.4. Synthetic protocol for the synthesis of dihydropyridines

In a typical one pot synthesis, 5,5-dimethyl-1,3-cyclohexanedione (2.0 mmol) and ammonium acetate (1.0 mmol), was added along with corresponding benzaldehyde derivatives (1.0 mmol) in an oven dried round bottom flask. To the above reaction mixture was added 100 mg of prepared transition metal based solid support catalyst. The reaction was kept at reflux in ethanol for about 4-6 h, until the starting materials disappeared. It was then cooled to ambient temperature, afterwards crushed ice was added to get precipitation. The resultant precipitate was washed by ethyl acetate (3×15 mL). Column chromatography was used where it was required for purifications. The dihydropyridines were obtained in solid form with different yields.

3,3,6,6-Tetramethyl-9-(*p*-tolyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)-dione (12a)

Pale orange colour solid, Yield 61%, 221 mg, M.P. 272-276 °C, (Lit. >250 °C) ^[11], IR v_{max} , cm⁻¹: (Solid, KBr) 3278 (NH), 1652, 1606, 1428, 1365. 1H NMR (400 MHz, DMSO- d_6): δ_{H} 9.22 (1H, brs N*H*), 7.02 (2H, d, J = 8.0 Hz, Ar*H*), 6.94 (2H, d, J = 8.0 Hz, Ar*H*), 4.75 (1H, s, C*H*-9), 2.44 (2H, d, J = 16.0 Hz, 2C*H*H), 2.31 (2H, d, J = 16.0 Hz, 2CHH), 2.17 (3H, s, Ar-

*CH*₃), 2.16 (2H, d, *J* = 16.0, 2*CH*H), 1.97 (2H, d, *J* = 16.0 Hz, 2*C*H*H*), 0.99 (6H, s, (*CH*₃)₂), 0.85 (6H, s, (*CH*₃)₂); EI-MS *m*/*z* 364.0 (M + H).

9-(2-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2*H*,5*H*)dione (12b)

Yellow colour solid, Yield 57%, 209 mg, M.P. 99-302 °C, (Lit. >300 °C) ^[12] IR v_{max} , cm⁻¹): (Solid, KBr) 3545, 3283 (NH), 1623, 1368. ¹H-NMR (400 MHz, DMSO-*d*₆): $\delta_{\rm H}$ 9.59 (1H, s, O*H*), 9.44 (1H, s, N*H*), 6.92 (1H, t, Ar*H*, *J* = 8.0 Hz), 6.86 (1H, app d, Ar*H J* = 8.0 Hz), 6.68-6.65 (2H, m, Ar*H*), 4.84 (1H, s, C*H*), 2.45 (4H, app q, (C*H*₂)₂ *J* = 16 Hz), 2.25 (2H, d, 2C*H*H *J* = 16.0 Hz), 2.07 (2H, d, 2CH*H*, *J* = 16 .0Hz), 1.01 (6H, s, (C*H*₃)₂), 0.88 (6H, s, (C*H*₃)₂). EI-MS, *m/z* (%). 365.1.

Molecular Docking Studies

The crystal structures of human carbonic anhydrase II (PDB id: 4qiy, 1.3 Å), IX (PDB id: 6g9u 1.7 Å) and XII (PDB id: 1jd0, 1.5 Å) were downloaded from the Protein Data Bank (PDB). All steps of ligand and receptor preparation (deletion of unwanted ligands, solvents molecules, addition of hydrogen and charges etc.) were carried out using default settings in BioSolveIT's LeadIT software (LeadIT version 2.3.2; BioSolveIT GmbH, Sankt Augustin, Germany, 2017, <u>www.biosolveit.de/LeadIT</u>). For each compound a total of 10 docked poses were generated, out of these HYDE (a utility of LeadIT software) analysis of each pose was carried out to find out the conformation with most favorable binding free energy, which was selected for detailed evaluation of binding site interactions. For 3D visualization of these binding site interactions Discover Studio Visualizer was used.

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