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Au-TiO_2NANOSPHERES CATALYZED ONE-POT-MCR SYNTHESIS, CHARACTERIZATION AND ANTI-PROLIFERATION ACTIVITY OF INDOLYL-IMIDAZOLO-PYRIDINES CARBOXYLIC ACID HYBRIDS

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ABSTRACT

In this context, we describe the efficiency of this catalyst towards green organic synthesis has been studied by carrying out a mixture of 1-fluoro-4-isocyanobenzene **(1)**, 6-aminonicotinic acid **(2)**and substituted 1H-indole-3-carbaldehyde **(3a-i)** in distilled water, porous Au/TiO_2nanospheres were added at room temperature in H_2O. It proceeds yielding the corresponding isubstituted-3-((4-fluorophenyl) amino)-2-(1H-indol-3-yl)imidazo [1,2-a]pyridine-6-carboxylic acid derivative in good to excellent yield viz one-pot multi-component reaction. All the title compounds were also screened for Anti- proliferation activity screened for their *in vitro* anticancer activity against four human cancer cell lines MCF-7, HeLa, HEK 293T and IMR 32. Among them 4a (having 4-OCH_3 substituent) has shown promising activity with IC_{50} (µM) 16.74±1.86 (MCF-7), 40.68 ± 1.25(HeLa), 50.61±4.64 (HEK 293T) and 26.58±1.68 (IMR32) has shown IC_{50} (µM) and these results are close to that of standard drug Doxorubicin.

Keywords: Indolyl-Imidazolo- Pyridines, Au-TiO_2 NPS, Anti- proliferation Activity

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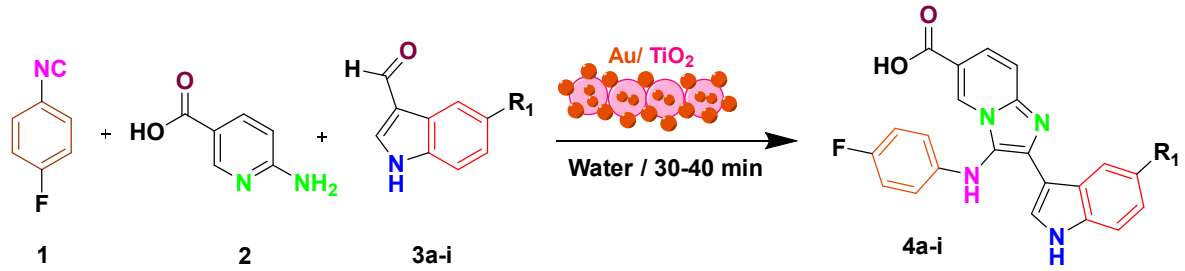
INTRODUCTION

Heterocycles with a vicinal diaryl replacement are a significant pharmacophore in therapeutic science and are key structure blocks for an assortment of mixtures showing anticancer and calming activities[1,2]. The cytotoxic properties of these mixtures are principally credited to tubulin hindrance through their calming action is transcendently evoked through the restraint of cyclooxygenase[3]. The two exercises require the diaryl pharmacophore with a cis-olefin configuration[4]. Henceforth, a few fragrant heterocyclic rings including five-membered like 1,2-diazacyclopenta-2,4-diene[5],1*H*-imidazole[6],1,2,5-oxadiazole[7], 1,2-oxazole[8],1,2,3-thiadiazole[9], triazole[10], six-membered as azabenzene azineand combined bicyclic rings, as pyrazolo[1,5-a]pyrimidines[11], quinazolinone[12], 1*H*-benzimidazole[15] , 1*H*-indole[16-19].Herewith we describe the one-pot synthesis of Indolyl-Imidazolo-Pyridine linkers is shown below(Scheme-1 and Fig.-1).



Scheme-1 One-pot MCR Synthesis of Indolyl-Imidazolo-Pyridine Linkers

EXPERIMENTAL

Preparation of porous titanium dioxide NSP's

Penetrable titanium dioxide nanospheres were prepared by a solvothermal procedure uncovered earlier.[13] Titanium tetraisopropoxide (10 ml) (Fluka, near 100 percent) was added drop-wise to 35 mL of refined ethanol with reliable blending wherein a smooth suspension was outlined immediately. 5 mL of twofold refined water was then added drop by drop to the suspension. After 2 h blending, the whole suspension

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was moved into a Teflon holder and kept in a tempered steel autoclave at 115 °C for 12 h. The ensuing white porous titanium dioxide nanospheres were detached through filtration and washed a couple of times with twin distinguished water, dried up at 100 °C for the departure of H_2O, ultimately calcined at 400 °C for 3 h.

Table-1: Analytical, LCMS Data of Newly Synthesized Compounds 4a-i

Entry	MF	LCMS: m/z	Analytical Data of CHN Analyzer	
			Found (%)	Calcd (%)
4a	$C_{23}H_{17}FN_4O_3$	416.13[M]$^{+\cdot}$	C,66.34;H, 4.11; N, 13.45	C,66.21;H, 4.04; N, 13.38
4b	$C_{23}H_{14}FN_5O_2$	411.11[M]$^{+\cdot}$	C, 67.15; H, 3.43; N, 17.02	C, 67.05; H, 3.23; N, 16.08
4c	$C_{23}H_{17}FN_4O_2$	400.13[M]$^{+\cdot}$	C, 68.99; H, 4.28; N, 13.99	C, 68.19; H, 4.18; N, 13.81
4d	$C_{22}H_{14}ClFN_4O_2$	420.80[M]$^{+\cdot}$	C,62.79; H, 3.35;N, 13.31	C,62. 71; H, 3.25;N, 13.21
4e	$C_{22}H_{14}F_2N_4O_2$	404.11 [M]$^{+\cdot}$	C,65.35; H, 3.49;N, 13.86	C,65.25; H, 3.26;N, 13.62
4f	$C_{24}H_{19}FN_4O_3$	430.14[M]$^{+\cdot}$	C, 66.97; H, 4.45; N, 13.02	C, 66.67; H, 4.35; N, 12.92
4g	$C_{25}H_{21}FN_4O_3$	444.16[M]$^{+\cdot}$	C, 67.56; H, 4.76; N, 12.61	C, 67.36; H, 4.46; N, 12.16
4h	$C_{22}H_{14}BrFN_4O_2$	467.21[M]$^{+\cdot}$	C, 56.79; H, 3.03;N, 12.04	C, 56.69; H,2.99;N, 12.01
4i	$C_{22}H_{14}FIN_4O_2$	512.28[M]$^{+\cdot}$	C, 51.58; H, 2.75;N, 10.94	C, 51.31; H, 2.45;N, 10.54

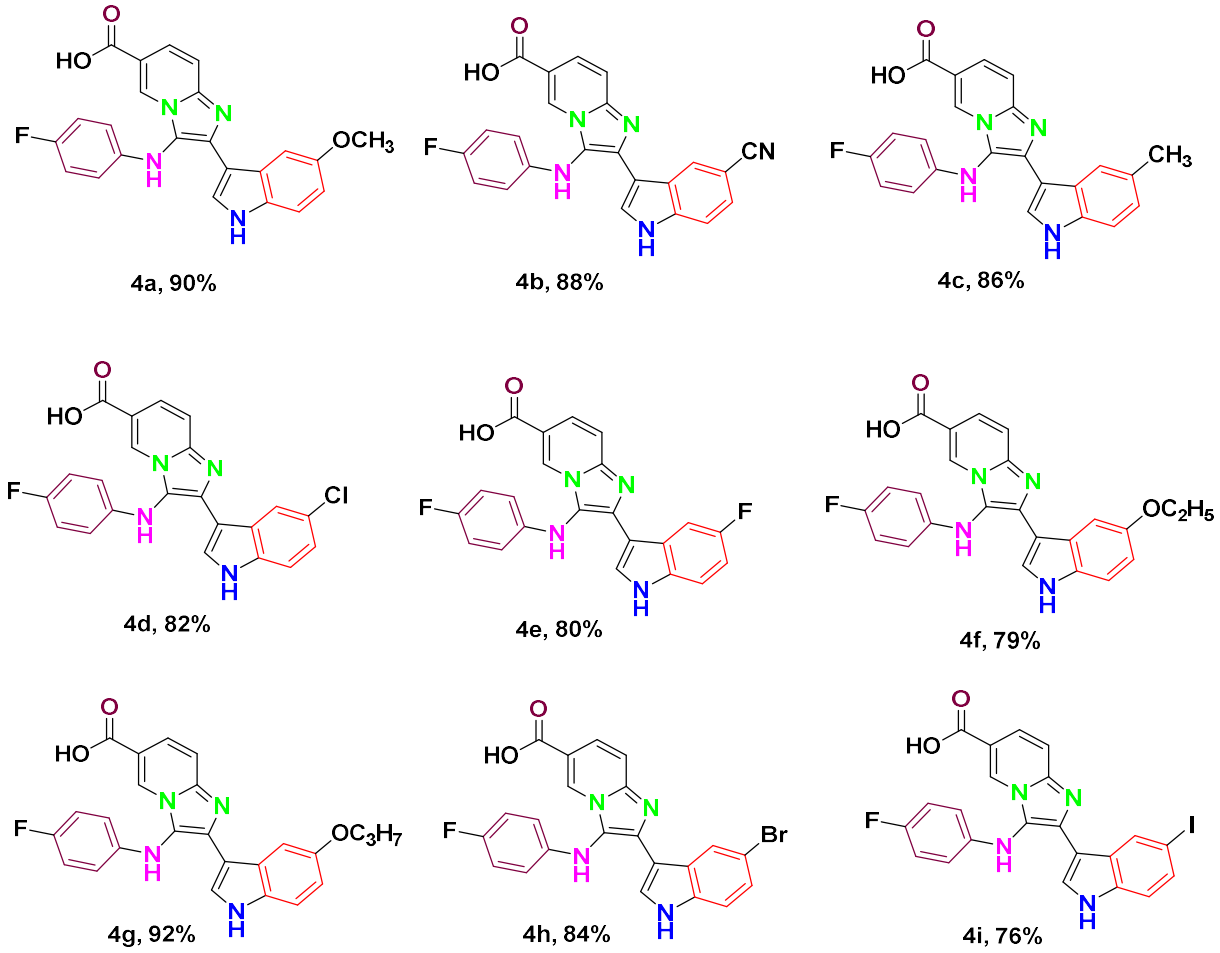

Fig.-1: Structures and Yield (%) of Title Compounds Indolyl-Imidazolo-Pyridine Linkers 4a-i

Synthesis of Au-TiO_2NSP's

The permeable Au/TiO2nanospheres were ready through the testimony precipitation method.[14] Accordingly, 100 mL of a watery arrangement of $HAuCl_4.3H_2O$ (1.02 mM) was warmed to 80 °C and the pH under 7 by the drop-wise expansion of NaOH (1 M). Subsequently, 1g of permeable titanium dioxide nanospheres were scattered in the above arrangement followed by correcting the pH to 7 with NaOH (0.2 M). The deferment was then warmed at 80 °C (in an oil shower) for 2 h with enthusiastic mixing. The

solids were assembled by centrifugation (12,000 rpm for 10 min), washed multiple times by mixing in hot (50 °C) refined water, and afterward centrifuged. Drying underneathvacuum at 100 °C for 2 h, they were calcined at 350 °C for 2 h to get the permeable Au/TiO_2NSP's.

Schematic Procedure for the Synthesis of Series of Various 3-((4-fluorophenyl) amino)-2-(1H-indol-3-yl) imidazo[1,2-a]pyridine-6-carboxylic acid hybrids (4a-4i)

To a combination of 1-fluoro-4-isocyanobenzene (1), 6-aminonicotinic corrosive (2), and subbed 1H-indole-3-carbaldehyde (3a-I) in refined water (10 ml), permeable Au/TiO_2nanospheres (2 mg) were added at RT. The response combination was warmed in a water shower for 40 min. After the consummation of the response, the response combination was cooled to room temperature. Then, at that point, the item was removed with a base measure of chloroform and dried over sodium sulfate. The product was solidified in chloroform-ethyl acetic acid derivation combination (3:2) to yield unadulterated series of different 3-((4-fluorophenyl) amino)- 2-(1H-indol-3-yl)imidazo[1,2-a]pyridine-6-carboxylic corrosive mixtures (4a-4i) as translucent strong. For the time-transformation studies, 200 µL of the response blend was removed at customary time spans and broke up in 1.8 mL of DCM from which 100 µL was infused into the HPLC section.

^{1}H NMR (400MHz, $CDCl_3$)Data of the Title Compounds 4a-4i

4a: δ 8.59 (s, 1H), 8.37 (s, 1H), 7.70 – 7.31 (m, 6H), 7.20 – 6.71 (m, 5H), 3.86 (s, 3H).
4b: δ 9.15 –8.81 (m, 2H), 8.65 (s, 1H), 8.18 (s, 1H), 7.99(d, 1H),7.72 –7.45(m, 3H),7.30(s, 1H),7.20 – 6.83 (m, 4H)
4c: δ 8.81 (s, 1H), 8.62 (s, 1H), 7.62 (dd, 4H), 7.37 (d, 1H), 7.28 – 6.76 (m, 6H), 0.81 (s, 3H).
4d: δ 8.82 (s, 1H), 8.64 (s, 1H), 8.00 – 7.53 (m, 3H), 7.26 (dd, 3H), 7.13 – 6.85 (m, 5H).
4e: δ 8.59 (s, 1H), 8.33 (s, 1H), 7.89 (d, 1H),7.70 –7.45 (m, 4H),7.42 –7.20 (m, 2H), 7.15 – 6.80(m, 4H).
4f: δ 8.59 (s, 1H), 8.36 (s, 1H), 7.51 (ddd, 6H), 7.16 – 6.80 (m, 5H), 4.10 (s, 2H), 1.43 (s, 3H).
4g: δ 8.54 (d, 1H), 7.89 – 7.37(m, 6H), 6.98 (dt, 5H), 6.21 (s, 1H), 4.03 (s, 2H), 1.84 (s, 2H), 1.01 (d, 3H).
4h: δ 8.82 (s, 1H), 8.64 (s, 1H), 8.12 (s, 1H), 7.60 (s, 2H), 7.45 – 6.73 (m, 8H).
4i: δ 8.59 (dd, 2H), 8.35 (s, 1H), 7.89 – 7.44 (m, 4H), 7.44 – 7.20 (m, 2H), 7.13 – 6.83 (m, 4H).

^{13}C-NMR (75MHz,$CDCl_3$)Spectra of Compounds 4a-4i

4a: δ 163.30, 154.66, 147.50, 137.68, 134.71, 134.28, 131.94.
4b: δ 167.15, 147.51, 140.11, 134.81,134.28,124.09, 123.46.
4c: δ 167.15,159.46, 147.52, 140.11, 137.68 , 135.07.
4d: δ 167.17, 159.46, 140.11, 136.78, 131.65, 126.67.
4e: δ 167.15, 167.15, 168.23, 142.59, 140.11, 134.81.
4f: δ 163.30,155.09, 140.11, 137.68, 134.81.
4g: δ 163.30, 154.67, 147.50, 140.11, 137.68, 134.83, 132.10.
4h: δ 167.13, 159.46,147.51,140.13, 137.65, 134.76, 131.65.
4i: δ 163.30, 145.76, 141.23, 140.14, 137.67, 131.38, 126.79,125.26.

RESULTS AND DISCUSSION

Anti-proliferation Activity

A series of various 3-((4-fluorophenyl)amino)-2-(1H-indol-3-yl)imidazo[1,2-a]pyridine-6-carboxylic acid hybrids **(4a-4i)** have been evaluated for their in vitro anticancer movement against four human malignant growth cell lines MCF-7, HeLa, HEK 293T and IMR 32 using Doxorubicin as standard. When we observe the results (Table 2), the compounds 4a, 4b, and 4d were active against four cell lines, and among them, 4b (having CN substituent) has shown more activity with IC50(µM) 26.38±2.58 (MCF-7), 45.78 ± 2.24 (HeLa), 60.86±5.24 (HEK 293T) and 36.58±2.18 (IMR32)has shown IC50(µM). Whereas 4d 32.38±1.58 (MCF-7), 55.78 ± 3.14 (HeLa), 65.86±6.04 (HEK 293T) and 44.58±2.42 (IMR32) and 4a (having 4-OCH_3 substituent) has shown promising activity with IC50 (µM) 16.74±1.86 (MCF-7), 40.68 ± 1.25 (HeLa), 50.61±4.64 (HEK 293T) and 26.58±1.68 (IMR32) have shown IC50(µM) and these results are close to that of reference drug Doxorubicin.

Table-2: *In vitro*Anticancer Activity of Synthesized Compounds (4a-4i) with IC50 in µM[a].

Entry	[b] MCF-7	[c] HeLa	[d] HEK 293T	[e] IMR32
4a	16.74±1.86	40.68 ± 1.25	50.61±4.64	26.58±1.68
4b	26.38±2.58	45.78 ± 2.24	60.86±5.24	36.58±2.18
4c	46.34 ± 4.86	89.85 ± 8.53	80.44±7.18	86.85 ± 8.13
4d	32.38±1.58	55.78 ± 3.14	65.86±6.04	44.58±2.42
4e	56.98 ± 4.32	80.44±7.18	89.85 ± 7.03	70.44±4.88
4f	65.28 ± 5.74	ND	78.84± 6.02	90.12±9.02
4g	76.14 ± 6.14	60.78 ± 4.14	76.24 ± 5.04	ND
4h	78.84± 7.02	58.22 ± 2.78	92.24±7.12	78.84± 5.82
4i	ND	94.24±9.02	83.61±6.27	68.14±3.75
Doxorubicin	12.76 ± 1.30	35.60±1.05	45.61±3.27	18.46±1.24

ND = Not determine. [a] Each data represents mean ±S.D values from three different experiments performed in triplicates. [b] MCF-7: human breast cancer cell line. [c] HeLa: human cervical cancer cell line. [d] HEK 293T: embryonic kidney cancer cell line. [e] IMR32: human neuroblastoma cell line.

CONCLUSION

Permeable TiO_2nanospheres were arranged to utilize a solvothermal strategy and used in the statement precipitation technique to manufacture permeable Au/TiO_2 nanospheres. It's worth adding that Au/TiO_2 can act as a functional impetus. 3-((4-fluorophenyl)amino)-2-(1H-indol-3-yl)imidazo [1, 2-a]pyridine-6-carboxylic acid hybrids series (4a-4i) with high yields was developed. The compounds 4a, 4b and 4d are active against four cancer cell lines (MCF-7, HeLa, and A549, HEK 293T and IMR32) and the results are comparable with that of standard Doxorubicin.

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