A MICROWAVE IRRADIATED FACILE AND CONVENIENT SYNTHESIS OF 6-PHENYLINDOLO[2,1-A]ISOQUINOLINE DERIVATIVES

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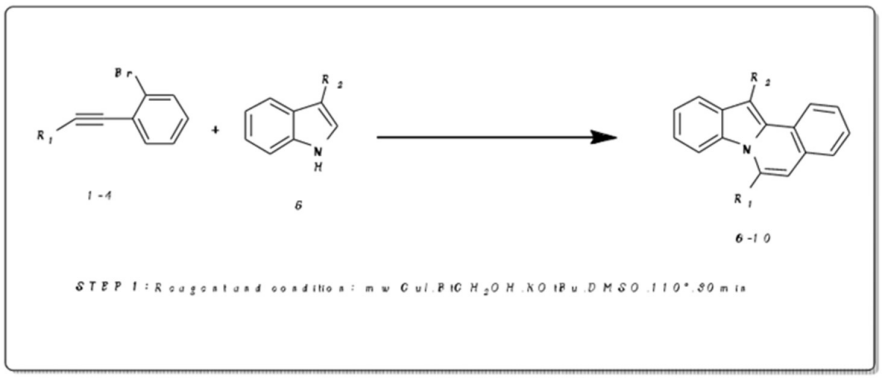
Abstract
Diversity-oriented, uncomplicated, proficient, microwave irradiated novel green procedure is developed for the quantitative synthesis of medicinally significant 6-phenylindolo[2,1-a]isoquinoline libraries. The present process is more convenient and competent as compared to other conventional processes.

Introduction:
Over the years, scientists have started investigate environmentally benign synthetic organic conversion. The green chemistry has concerned the concentration of the academia as well as industry. Research for finding other alternating reaction media, which can replacement, the harmful, toxic, and inflammable organic solvents, which pose a serious threat to the environment, is gaining much progress. In view with this perspective, the development of newer synthetic strategies with greener perspectives is indisputably appealing to accomplish more sustainable chemistry. In addition, if the new reaction media, catalysts and alternative energy resource can independently or in a synergistic approach can provide some additional merits on the reaction performance such as on the reactivity, catalyst efficiency, and catalyst reuse when applied, then this can certainly be very interesting.
Microwave assisted chemical synthesis expansion is at the present time a well successful technique for synthesis of a variety of organic compounds. It has emerged as a powerful synthetic tool to speed up a wide range of chemical reactions. The remarkable results are obtained including remarkably cutting the required time, improving the yields, experimental simplicity, selectivity, purity of the desired products and easy work up etc. were obtained giving clear suggestion on the potentialities of this technique than reactions under conventional heating.

Extensive studies have demonstrated that isoquinoline and there analogues exhibit various pharmacological activity including Anticancer, Antibacterial and Antiinflamatory. The unique structure together with a potential therapeutic function of isoquinoline has sparked much interest among synthetic chemist. We have synthesized tetracyclic isoquinoline derivatives to optimize their biological activities.

RESULTS AND DISCUSSION:
In the first step commercially available 4-iodoanisole was reacted with 2-methyl-3-butyne-2-ol, palladium catalyst, copper iodide, triethylamine as base and solvent under nitrogen atmosphere at room temperature. 2-iodobromobenzene reacts with different phenylacetylene derivative under Sonogashira coupling condition to form the 1-bromo-2-(phenylethynyl)benzene derivatives under N2 atmosphere. The 1-bromo-2-(phenylethynyl)benzene derivatives reacts with 3-methyl indole, through C-2 arylation in the presence of benzotriazole methanol as ligand to form 6-phenylindolo[2, 1- a]isoquinoline derivatives.

Final synthesized compounds



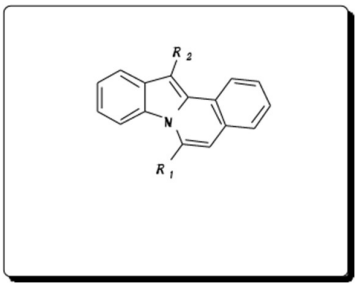


Table-I

Compound	R1	R2	Yield%
6	4-methoxyphenyl	-methyl	44
7	4-methylphenyl	- methyl	46
8	4-fluorophenyl	- methyl	45
9	2-pyridyl	- methyl	45
10	Phenyl	-hydrogen	54

CONCLUSION: In summary, we have reported an exceptionally efficient green approach for the synthesis of of 6-phenylindolo[2,1-a]isoquinoline via microwave-assisted synthesis. This synthetic approach has a variety of excellent characteristics such as excellent yields, less reaction time, recyclability of catalyst and operational simplicity, ultimately foremost to a diverse array of medicinally-relevant of 6-phenylindolo[2,1-a]isoquinoline ring systems.

EXPERIMENTAL

Commercially available reagent grade chemicals were purchased from Sigma-Aldrich or Spectrochem Pvt Ltd and were used as received. Melting points were taken in open capillaries on an electrically heated melting point apparatus complab and are uncorrected. IR spectra were recorded on perkin- elmer RX-1 spectrophometer using KBr pallets. The FAB spectra were recorded using a beam of argon (2-8eV) on joel SX 102/ DA-6000 mass spectrometer, 1H NMR and 13C NMR spectra were

recorded on bruker DPX-200 (200 MHz for 1H and at 50 MHz for 13C) or DRX-300 (300 MHz for 1H and at 75 MHz for 13C) spectrometers using CDCl3, DMSO-d6 and CD3OH as solvent. Tetramethylsilane served as an internal standard in 1H NMR and CDCl3 in 13C spectra. Silica gel (60-120 mesh) was used for column chromatography while silica gel (230-400 mesh) was used for flash chromatography. TLC was run either on precoated silica gel 60F 254 and RP-18 F 254 (merck) or handmade plates. Detection of spots was done either by iodine vapors or spraying with 1% ceric sulfate in 1M H2SO4 followed by heating at 110ºC.

General experimental procedure for the Synthesis of 6-phenylindolo[2, 1-a]isoquinoline derivatives:

To the stirring mixture of copper iodide (5mol%), Benzotriazole methanol(10 mol%) the N-heterocycle(1mmol) and 1.1 equivalent of 2-haloarylalkyne was added and followed by addition of base potassium tertiary butoxide (1.4 eq), degassing with N2 atmosphere for 10 min. Then add Dimethyl sulphoxide (2 ml) by syringe, reaction mixture was heated to 110ºC in microwave until 2-haloarylalkyne had been completely consumed. The reaction mixture was extracted using ethyl acetate and water. Ethyl acetate layer was concentrated under reduced pressure. Crude obtained was purified by flash chromatography Hexane as eluent to give compounds (6-10).

6-(4-methoxyphenyl)-12-methylindolo [2,1-a] isoquinoline(6): Chemical formula: C24H19NO MW: 337, State: Yellow solid, MP: 145ºC, Yield: 44% , MS (ESI) m/z (M+H): 338.19 1H NMR(300 MHz, CDCl3): : 8.47-8.44(d, J=7.56Hz, 1Hz), 7.83-7.80(d, J=7.98Hz, 1H), 7.56-7.44(m, 5H), 7.10-7.07(d, J=8.46Hz, 3H), 6.97-6.95(d, J=7.8Hz, 1H), 6.53-6.50(d, J=8.7Hz, 1H), 6.45(s, 1H), 3.96(s, 3H), 2.91(s, 3H). 13C(CDCl3, 50MHz): : 160.28, 138.28, 131.52, 130.24, 129.33, 128.44, 12.25, 126.69, 126.19, 124.43, 121.04, 120.32, 118.06, 114.44, 114.28, 110.89, 105.45, 55.46, 11.89.

12-methyl-6-p-tolylindolo [2, 1-a] isoquinoline(7): Chemical formula: C24H19N, MW: 321, State: Sticky oily, Yield: 46%, MS (ESI) m/z (M+H): 322.13 1H NMR(300 MHz, CDCl3): : 8.48-8.45(d, J=7.98Hz, 1H), 7.83-7.81(d, J=7.92Hz, 1H), 7.54-7.36(m, 8H), 6.97-6.92(t,J=8.31Hz, 1H), 6.52-6.46(t, J=8.61Hz, 2H), 2.92(s, 3H), 2.54(s, 3H).

6-(4-fluorophenyl)-12-methylindolo [2, 1-a] isoquinoline(8): Chemical formula: C23H16FN, MW: 325, State: Oily, Yield: 45%, MS (ESI) m/z (M+H): 326.07, 1H NMR(300 MHz, CDCl3): : 7.71-7.51(m,8H), 7.36-7.18(m, 5H), 2.42(s, 3H). 13C(CDCl3, 50MHz): :14.10, 135.70, 133.11, 132.99, 132.50, 129.45, 127.07, 125.66, 125.03, 123.42, 122.68, 120.16, 119.34, 113.66, 110.42, 9.59.

12-methyl-6-(pyridin-2-yl)indolo[2,1-a]isoquinoline(9): Chemical formula: C22H16N2, MW: 308, State: Oily, Yield: 45%, MS (ESI) m/z (M+H): 309.15, 1H NMR(300 MHz, CDCl3): : 8.65- 8.64(d, J=4.02Hz, 1H), 7.70-7.58(m, 7H), 7.34-7.22(m, 5H), 2.17(s, 3H)

6-phenylindolo[2,1-a]isoquinoline(10): Chemical formula: C22H15N, MW: 293, State: Oily Yield: 54% MS (ESI) m/z (M+H): 294.4 1H NMR(300 MHz, CDCl3):: 8.26-8.24(d, J=7.35Hz, 1H), 7.83-7.80(d, J=7.80Hz, 1H), 7.60-7.47(m, 8H), 7.39(s, 1H), 7.25-7.20(t, J=7.26Hz, 1H), 6.94-6.89(t, J=7.38Hz, 1H), 6.56(s, 1), 6.48-6.45(d, J=8.16Hz,1H).

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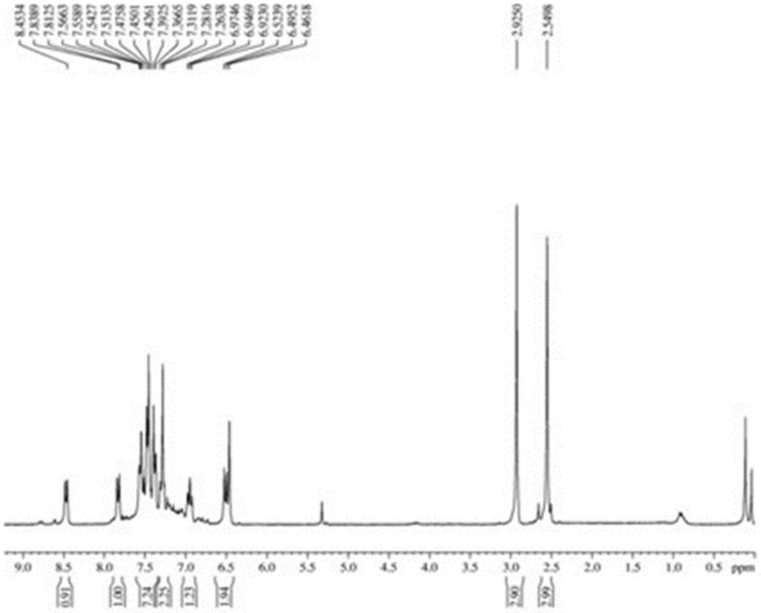
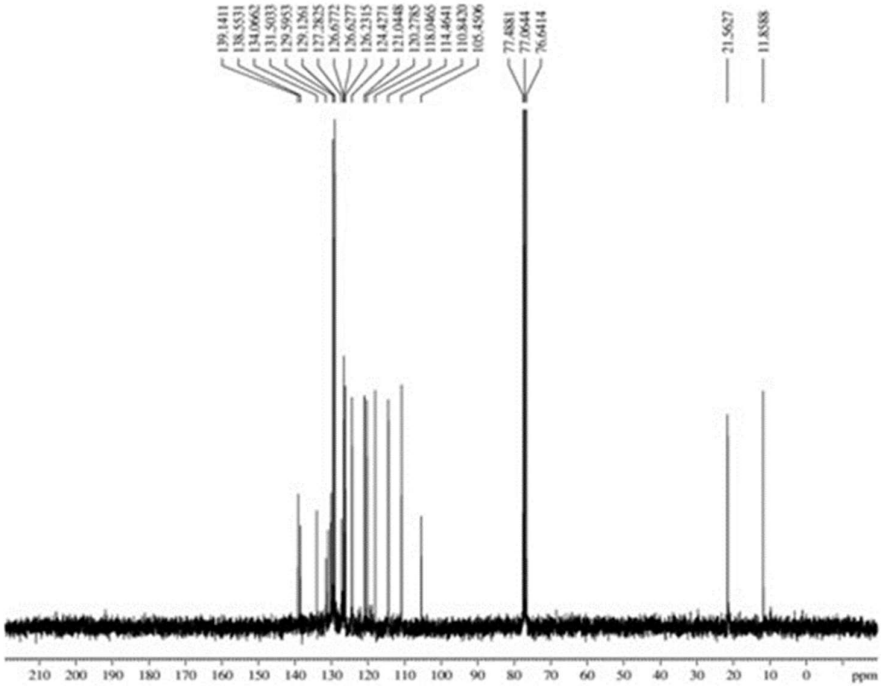


1H NMR of compound 7



13C NMR of compound 7