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Microwave assisted synthesis of pharmacologically active N-phenyl acetamide derivatives of indolo [2, 3-b] quinoxaline

Krishnakant T.Waghmode[1], Nandini R.Pai[2]

[1](Department of Chemistry, D.G.Ruparel College/ University of Mumbai, India)
[2](Department of Chemistry, D.G.Ruparel College/ University of Mumbai, India)

ABSTRACT
We have developed rapid and efficient method for the synthesis of pharmacologically active N-phenyl acetamide derivatives of indolo [2, 3-b] quinoxaline by using microwave irradiations. Condensation of Substituted phenyl iodoacetamide derivatives with indolo [2, 3-b] quinoxaline under the influence of microwave radiations gave the products. Microwave assisted synthesis not only reduced the reaction time drastically but also gave excellent yields of N-phenyl acetamide derivatives of indolo [2, 3-b] quinoxaline.

Keywords - Excellent yields, Indolo [2, 3-b] quinoxaline, Phenyl iodoacetamides, Microwave irradiations.

I. INTRODUCTION
Literature survey has revealed that N-substituted indolo [2, 3-b] quinoxiline derivatives are pharmaceutically active. Several attempts has been made to synthesize the N-substituted derivatives of indolo [2, 3-b] quinoxiline. N-phenyl acetamide derivatives of pyrazole shows local anesthetic and anti-arrhythmic activities.[1] According to findings by Lofgren, a local acetanilide anesthetic, such as lidocaine, should contain a lipophilic aromatic structure, a tertiary hydrophilic amino group, and between these two moieties an anesthesiophoric group (ester, ether, amino, carbonyl, amide).[2-4] Usually, an amide as the anesthesiophoric group provides higher activity.[2]
Microwave radiation has proved to be a highly effective heating source in chemical reactions. Microwaves can accelerate the reaction rate, provide better yields and uniform and selective heating, achieve greater reproducibility of reactions and help in developing cleaner synthetic routes.
Some new 6-(aryl amino acetyl) indophenazine derivatives were prepared by Yanni Amals and Abdel Rehman.[5] The product showed antibacterial activity.

Hence, in the present investigation, we decided to synthesize N-substituted derivatives of indolo [2, 3-b] quinoxiline under the influence of microwave irradiations by using domestic microwave oven.

II. MATERIALS AND METHODS:
All commercial reagents were used as received without purification, and all solvents were of reagent grade. Reactions were carried out in domestic microwave oven (Samsung model). The reaction was monitored by TLC using 0.25 mm E-Merck silica gel 60 F254 precoated aluminium plates, which were visualized with UV light. Melting points were taken in open capillaries. The IR spectra were recorded on a Perkin-Elmer 257 spectrometer using KBr discs.[1]H NMR spectra in DMSO-d6 were recorded on VXR-200,300 and 400 MHz using TMS as internal standard.

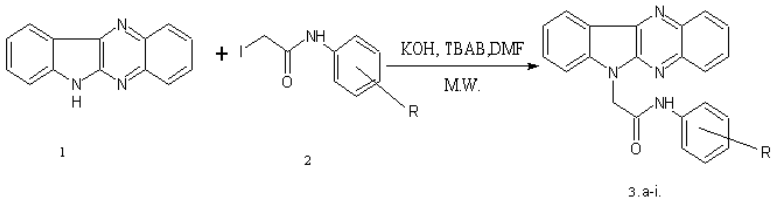
Synthesis of Indolo [2, 3-b] quinoxaline
Indolo [2, 3-b] quinoxaline (3) was prepared by refluxing 0.05 mol of isatin (1) with equivalent amount of ortho-phenylene diamine (2) in glacial acetic acid.[6]
Substituted 2-iodo-N-phenyl acetamides (2) were obtained from substituted 2-chloro-N-phenyl acetamide with sodium iodide in acetone under reflux condition.[7]

Microwave assisted synthesis of 3a-i:
An intimate mixture of indoloquinoxaline(1) 1 mmol, the appropriate substituted 2-iodo-N-phenyl acetamides (2) 1.1 mmol, KOH 1.3 mmol, catalytic amount of tetrabutyl ammonium bromide and some drops of dimethyl formamide (giving slurry at room temperature) was exposed to MW irradiation. Completion of the reaction was checked with TLC(ethyl acetate-n-hexane 8:2), microwave powers, times and yields are listed in Table 1. The reaction mixture was cooled to room temperature

and mixed thoroughly with ice-water. Separated solid was filtered dried and recrystalized with dimethyl formamide. Same procedure was followed for the synthesis of 3a-i.

Reaction scheme:

Fig. 1. Reaction scheme for microwave assisted synthesis of N-substituted derivatives of indolo [2, 3-b] quinoxiline



Where R= H, CH_3, OCH_3, C_2H_5, F, Cl, etc.

Table-1. Microwave power, reaction times and yields for the synthesis of N-phenyl acetamide derivatives of indolo [2, 3-b] quinoxaline under MW irradiation

Entry	R	Microwave power in watt	Time in min.	% yield
3a	H	450	5	81
3b	2-C_2H_5	300	7	76
3c	2-OCH_3	300	5	86
3d	3-Cl-2-CH_3	450	5	78
3e	2-F	450	7	75
3f	2,6-di-C_2H_5	450	6	80
3g	2,5-di-Cl	450	7	71
3h	2,4-di-Cl	450	7	91
3i	3-Cl, 4-F	450	8	82

III. RESULTS AND DISCUSION:

We initially examined reactions under "dry" conditions.[8] Irradiating the mixture of neat reactants, decomposition of reactants or recovery of unreacted starting material was observed. On the other hand, results improved notably when some drops of a polar aprotic solvent, enough to humidify the reaction mixture, are added, giving a polar mixture that is more prone to MW

absorption[9]. This is a fundamental requirement in the case where the sodium salts of indoloquinoxaline or alkylation agents with high melting point are used. The reaction was also tried with K_2CO_3 as a base but it resulted into lower yields.

IV. CONCLUSION:

We have developed a simple and efficient MW assisted synthesis of pharmaceutically active N-phenyl acetamide derivatives of indoloquinoxaline by using a household oven. The procedure involves the use of KOH and a few drops of DMF. The use of MW irradiation offers many advantages: it remarkably decreases reaction times, requires less solvent, thus facilitating reaction workups, and increases yields.

V. Spectroscopic characterization data:

3a. N-phenyl-2-(6H-indolo [2,3-b]quinoxalinyl) ethanamide: m.p. >250 ^{0}C ;
IR(KBr):3301,3055,3016,1666,1596,1535,1411,1203,1010,748 cm^{-1} ; ^{1}H NMR(DMSO-d_6) 400MHz: δ 10.46(1H,s,NH), 8.42-41(1H,d,Ar-H), 8.31-29(1H,d,Ar-H), 8.11-09(1H,d,Ar-H), 7.82-76(4H,m,Ar-H),7.59-57(2H,d,Ar-H),7.44(1H,s,Ar-H),7.30(2H,s,Ar-H),7.064(1H,sAr-H),5.39(2H,s,CH_2), MS:- m/z = 352(m^+)

3b. N-2-ethyl phenyl-2-(6H-indolo [2,3-b]quinoxalinyl) ethanamide: mp. =220-223 ^{0}C ;
IR(KBr):3255,3055,1658,1620,1589,1527,1465,1203,1056,748 cm^{-1} ; ^{1}H NMR(DMSO-d_6) 300MHz: δ 9.85(1H,s,NH), 8.37-34(1H,d,Ar-H), 8.27-24(1H,d,Ar-H), 8.09-06(1H,d,Ar-H), 7.81-69(4H,m,Ar-H),7.60-57(1H,d,Ar-H),7.37-15(4H,m,Ar-H), 5.41(2H,s,CH_2)

3c. N-2-methoxy phenyl-2-(6H-indolo [2,3-b]quinoxalinyl) ethanamide: mp. =215-218 ^{0}C ;
IR(KBr):3301,3055,3016,1666,1596,1535,1411,1203,1010,748 cm^{-1} ; ^{1}H NMR(DMSO-d_6)400MHz: δ 10.46(1H,s,NH), 8.42-41(1H,d,Ar-H), 8.31-29(1H,d,Ar-H), 8.11-09(1H,d,Ar-H), 7.80-76(3H,m,Ar-H),7.59-57(2H,d,Ar-H),7.44(1H,s,Ar-H),7.30(1H,s,Ar-H),7.06(1H,sAr-H),6.82(1H,S,Ar-H),5.39(2H,s,CH_2), 3.85(3H,s,CH_3)

3e.N-3-chloro-2-methylphenyl-2-(6H-indolo[2,3-b]quinoxalinyl) ethanamide: mp.>250 ^{0}C ; IR(KBr):3221,3062, 1658,1581,1535,1411,1195,1018,756 cm^{-1} ; ^{1}H NMR(DMSO-d_6) 200MHz: δ 10.05(1H,s,NH), 8.55-52(1H,d,Ar-H), 8.41-31 (3H,m,Ar-H),8.14-12(1H,d,Ar-H),7.89-63(4H,m,Ar-H),7.26-22(1H,d,Ar-H),7.05-01(2H,m,ArH),5.40(2H,s,CH_2),2.27(3H,S,CH_3)

3e.N-2-fluoro phenyl-2-(6H-indolo [2,3-b]quinoxalinyl) ethanamide: mp. >250 ^{0}C ; IR(KBr):3221,3062, 1658,1581,1535,1411,1195,1018,756 cm^{-1} ; ^{1}H NMR(DMSO-d_6) 200MHz: δ 10.05(1H,s,NH), 8.40-36(1H,d,Ar-H), 8.31-29(1H,d,Ar-H), 8.11-02(1H,d,Ar-H), 7.82-57(4H,m,Ar-H),7.44-14(3H,m,Ar-H),5.40(2H,s,CH_2)

3f.N-2,6-diethyl phenyl-2-(6H-indolo [2,3-b]quinoxalinyl) ethanamide: mp.>250 ^{0}C ; IR(KBr):3255,3055, 1658,1589,1535,1411,12035,1118,748 cm^{-1} ; ^{1}H NMR(DMSO-d_6) 200MHz: δ 9.62(1H,s,NH), 8.36-20(2H,m,Ar-H), 8.06-02 (1H,m,Ar-H), 7.79-65(3H,m,Ar-H), 7.58(1H,d,Ar-H),7.38-34(2H,m,Ar-H),7.08-00(2H,m,Ar-H),5.36(2H,s,CH_2),2.49(4H,t,$(CH_2)_2$), 1.11-1.07(6H,t,$(CH_3)_2$)

3g.N-2,5-dichlorophenyl-2-(6H-indolo[2,3-]quinoxalinyl) ethanamide: mp.>250 ^{0}C ; IR(KBr):3247,3062, 1674,1581,1519,1473,1195,1010,756 cm^{-1} ; ^{1}H NMR(DMSO-d_6) 200MHz: δ 10.20(1H,s,NH), 8.55-52(1H,d,Ar-H), 8.41-34 (2H,m,Ar-H), 8.15-12(1H,d,Ar-H), 7.89-63(4H,m,Ar-H),7.42-38(2H,m,Ar-H),7.20-18(1H,m,Ar-H),5.49(2H,s,CH_2)

3h.N-2,4-dichlorophenyl-2-(6H-indolo [2,3-]quinoxalinyl) ethanamide: mp. =217-219 ^{0}C ; IR(KBr):3247,3062, 1674,1581,1519,1473,1195,1010,756 cm^{-1} ; ^{1}H NMR(DMSO-d_6) 200MHz: δ 10.20(1H,s,NH), 8.40-24(3H,m,Ar-H), 8.06 (1H,m,Ar-H), 7.81-68(3H,m,Ar-H), 7.58-54(1H,m,Ar-H),7.45-25(3H,m,Ar-H,5.47(2H,s,CH_2)

3i: N-3-chloro-4-fluoro phenyl-2-(6H-indolo [2,3-b]quinoxalinyl) ethanamide:- mp. =232-35 ^{0}C ; IR(KBr):3286,3055, 1674,1533,1203,1118,1010,871,748 cm^{-1} ; ^{1}H NMR(DMSO-d_6)200MHz: δ 10.73(1H,s,NH), 8.40-37(1H,d,Ar-H), 8.29-25 (1H,d,Ar-H), 8.08-05(1H,d,Ar-H), 7.86-73(5H,m,Ar-H),7.44-31(3H,m,Ar-H,5.38(2H,s,CH_2).

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