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Research Article

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Conventional and greener approach for the synthesis of some pharmacologically active derivatives of thiazolidines substituted with indolo [2,3-*b*]quinoxalines

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ABSTRACT

In the present study Indolo[2,3-b]quinoxalin-1-yl-N(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamide derivatives were synthesized from N'-benzylidene-2-(6H-indolo [2,3-b] quinoxalin-6-yl) acetohydrazide derivatives by conventional method and under microwave irradiation. N'-benzylidene-2-(6H-indolo [2,3-b] quinoxalin-6-yl) acetohydrazide derivatives were synthesized from Indolo [2,3-b] quinoxalin-6-yl) acetohydrazide. The compounds obtained were purified by column chromatography using silica gel. The chemical structures of the compounds were confirmed using IR, ^{1}H-NMR and mass spectroscopy.

Keywords: Thiazolidinone, Schiff bases, Microwave irradiations, Thioglycolic acid, Indolo [2, 3-b] quinoxaline.

INTRODUCTION

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring.

The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. The 4-thiazolidinone ring system is a core structure in various synthetic pharmaceutical agents, displaying a broad spectrum of biological activities such as, anti-tubercular[1a-b], anti-bacterial[2a-c] , anti-HIV[3], anti-inflammatory[4], anti-mycobacterial[5], anti-convulsant[6], anti-histaminic[7], anti-cancer[8], anti-protozoan[9] and analgesic[10] .

Several methods for synthesis are available in literature which involve conventional one pot, two pot synthesis[11-12] and microwave as well as combinatorial syntheses methods. The dithiocarbamates formed by the reaction of primary amine with carbon disulfide in the presence of base react with haloalkanoic acid in the presence of $NaHCO_3$ to give substituted 2-thiono-4-thiazolidinones.

The synthesis of 2-imino-4-thiazolidinones has been reported by using thiourea and sodium salt of labeled monochloroacetic acid[13], Another method of synthesis of 4- thiazolidinones is by use of thiocyanate,alkyl isothiocyanate with hydrazide/acetamide followed by the treatment with ethyl bromoacetate and sodium acetate[14] . Schiff's bases obtained by the condensation of ketones and amines also react with mercaptoacetic acid to give 2,2-disubstituted-4-thiazolidinones[15]. Desai KR *et al* [16] has carried out the microwave assisted synthesis of thiazolidinone from the Schiff's bases by using thiolactic acid. The products were synthesized by conventional and microwave synthesis and the yield were compared with each other. They concluded that the percent yield with the microwave irradiated synthesis was better than the conventional.

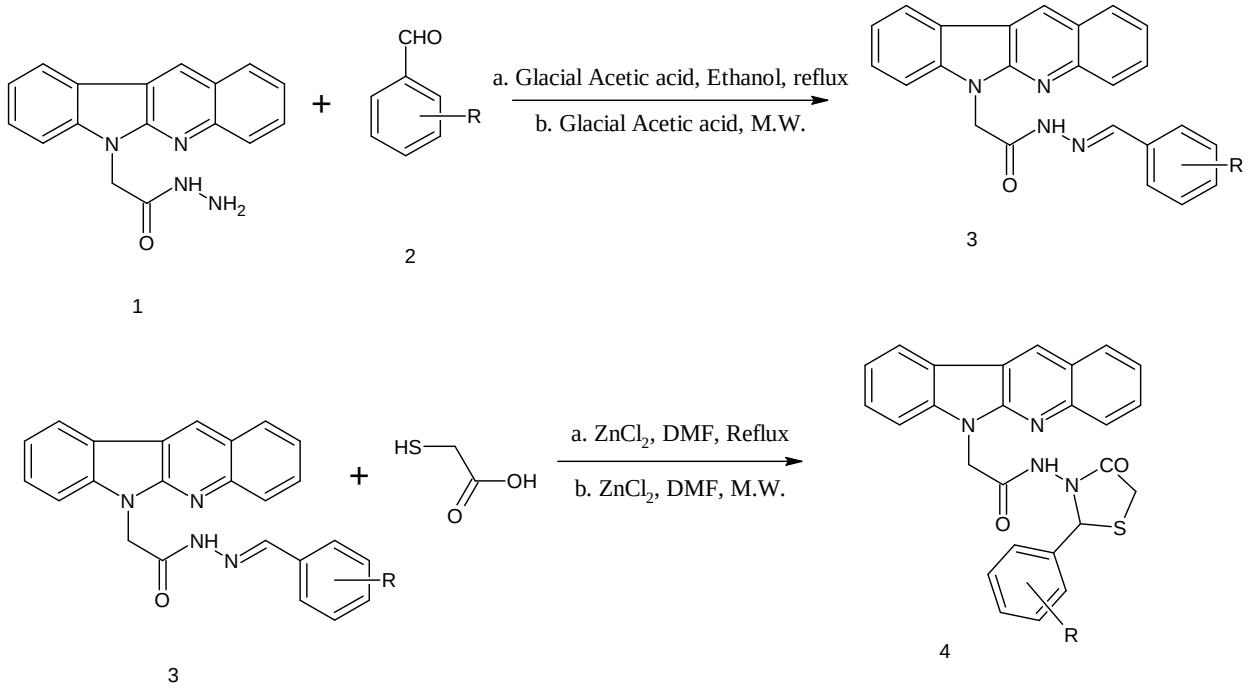
Use of task specific ionic liquid as synthetic equivalent of ionic liquid phase matrices for the synthesis of small library of 4-thiazolidinone is also possible. Ethylene glycol is functionalized in good yields with 4-(formylphenoxy) butyric acid by using DCC / DMAP catalyst. The synthesis was performed by one pot three component condensation under microwave dielectric heating[17-18]. Lot of Attempt to synthesize combinatorial libraries of 4-thiazolidinones are present in the literature as reported by *Look GC et al.* [19]

Synthesis of Schiff's bases of indophenazine derivatives as possible antipsychotic and anti-inflammatory agent has been reported by the conventional heating [20].

The aim of the present work was to synthesize new Thiazolidinone derivatives containing Indolo[2,3-b]quinoxaline moiety under the conventional heating and microwave heating conditions.

Reaction scheme:

The generalized reaction is shown in **Fig. I.**



Where R= -H, 3-NO_2, -CH_3, -OH, 2-Cl, -$N(CH_3)_2$

Fig. I: Reaction scheme

EXPERIMENTAL SECTION

General information: All air reactions were carried out in oven dried (120ºC) or flame dried glassware. Microwave reactions were carried out in domestic microwave oven (Samsung model) Analytical thin layer chromatography was performed with Merck silica gel plates (0.25mm thickness) with PF_{254} indicator. Compounds were visualized under UV lamp. Column chromatography was carried out using 60-120 mesh silica gel and technical grade solvents. ^{1}H-NMR spectra were recorded on at 200,300 and 400 MHz instruments with tetramethylene silane as an internal standard. IR spectras were recorded on Shimadzu Hyper IR instrument.

Experimental Procedure:-

In our previous work we have reported the synthesis of N'-benzylidene-2-(6H-indolo [2,3-b] quinoxalin-6-yl) acetohydrazide derivatives under conventional and microwave heating[21].

Synthesis of N'-benzylidene-2-(6H-indolo [2,3-b] quinoxalin-6-yl) acetohydrazide: 3a-f:

a. Conventional heating:

In a round bottom flask, Indolo [2,3-b] quinoxalin-6-yl) acetohydrazide (0.01 mol) and Substituted aromatic aldehydes (0.01mol), few drops of acetic acid were taken in ethyl alcohol and stirred with heating till the completion of the reaction. Progress of the reaction was checked with hexane-ethyl acetate 8:2. Then it was cooled and added with ice-cold water. It was filtered, washed with water and purified by recrystallization through glacial acetic acid. All the remaining compounds 3a to 3f were synthesized by similar procedure

b. Microwave heating:
In a hard glass tube, Indolo [2,3-b] quinoxalin-6-yl) acetohydrazide (0.01 mol) and Substituted aromatic aldehydes (0.01mol), few drops of acetic acid were taken and mixed well to prepare a paste. This mixture was irradiated in microwave till the completion of the reaction. Progress of the reaction was checked with TLC (hexane-ethyl acetate 8:2). After the completion of reaction, reaction mixture was cooled to room temperature and ice-cold water was added to it. It was filtered, washed with water and purified by recrystallization through glacial acetic acid. Same procedure was followed for the synthesis of compound 3a to 3f.

Synthesis of Indolo [2, 3-b] quinoxalin-1-yl-N (4-oxo-2-phenyl-1,3-thiazolidin-3-yl)acetamide:
a. Conventional heating;
In a round bottom flask, 3a. (0.01 mol) and thioglycolic acid (0.015mol) were taken in DMF, a pinch of $ZnCl_2$ was added as a catalyst. This mixture was stirred with heating for 10 hours. Progress of the reaction was checked with thin layer chromatography Chloroform-methanol 9:1. Then it was cooled and added with ice-cold water and triturated with an excess of 10% sodium bicarbonate solution. The product obtained was filtered, wash several times with water and separated by column chromatography. Same procedure was followed for the synthesis of compound 4a to 4f.

b. Microwave heating:
In a hard glass tube 3a (0.01 mol) and thioglycolic acid (0.01mol), a pinch of $ZnCl_2$ was added as a catalyst, few drops of DMF were added and mixed well to prepare a paste This mixture was irradiated in microwave till the completion of the reaction. Progress of the reaction was checked with Chloroform-methanol 9:1. After the completion of reaction, reaction mixture was cooled to room temperature and ice-cold water was added to it and triturated with an excess of 10% sodium bicarbonate solution. The product obtained was filtered, washed several times with water and separated by column chromatography. All the remaining compounds 4a to 4f were synthesized by similar procedure. Results are summarized in **table-I.**

Spectral Interpretation of Synthesized Compounds:
Compound (4a) IR (KBr): 3209(-NH str.),3062(Ar-CH str., 1681(>C=O, thiazolidine ring) 1675((-CONH-str.),1589, 1488, 1411, 1203,756 , cm^{-1}; ^1H NMR (200 MHz, DMSO-d^6) δ(ppm): 11.92 (1H,s, NH), 8.43-8.40(1H,d, Ar-CH) 8.32-8.27(1H,d, Ar-CH),8.12-8.10(1H,d,Ar-CH), 7.86-7.68(6H,m,Ar-CH),7.47-7.42(5H,m,Ar-CH), 6.12(1H, s, CH), 5.75(2H,s,CH2),3.83-3.73(2H,dd,CH_2)
MS:- m/z = 453(m^+)

Compound (4b):IR (KBr): 3332, (-NH str.), 1681, (>C=O, thiazolidine ring),1581 (C=C), 1488 (C-N), 1334 (CH), 1280,1203,1010 (C-C), 941, 748 (CH), 694 (CH), cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d^6:δ(ppm):12.024(1H,s,NH), 8.61(1H,d,Ar-CH)8.41-8.37(1H,d, Ar-CH),8.29-8.22(2H,d,Ar-CH), 8.06(1H,s,Ar-CH),7.81-7.69(6H,m,Ar-CH), 7.41(2H,t, Ar-CH),6.12(1H,s,CH), 5.79(2H,s,CH2),3.75-3.55(2H,dd,CH_2)

Compound (4c) N'-4-methyl benzylidene-2-(6H-indolo [2,3-b]quinoxalin-6-yl) acetohydrazide: mp.>250 0C; IR (KBr): 3186 (NH), 3039,1681(>C=O, thiazolidine ring),1581 (C=C), 1496 (C-N), 1280,1203,1118 (C-C), 948, 748, cm^{-1}; ^{1}H-NMR (200 MHz, DMSO-d6) δ(ppm): 11.56 (1H,s, NH),8.40-8.36(1H,d,Ar-CH) 8.29-8.26(1H,d, Ar-CH),8.18-8.08(1H,d,Ar-CH),7.84-7.69(4H,mAr-CH), 7.57-7.41(4H,m,Ar-CH), 7.21-7.19(2H,m,Ar-CH), 6.24(1H,s, CH), 5.68(2H,s,CH_2),3.70-3.54(2H,dd,CH_2), 2.22(3H,s,Ar-CH_3)

Compound(4d); IR (KBr): 3332(Ar-OH str.), 3201(NH str.), 3062 ,1681 1581, 1498, 1334 , 1288,1203,763, cm-1; ^{1}H NMR (400 MHz, DMSO-d6) δ(ppm): 11.59(1H,s, NH), 9.92(1H,s, Ar-OH),8.40-8.37(1H,d,Ar-CH) 8.30-8.29(1H,d, Ar-CH),8..26-8.25(1H,d,Ar-CH), 7.98-7.81(4H,m,Ar-CH), 7.75-7.61(2H,t,Ar-CH), 7.57-7.38(2H,m,Ar-CH), 6.83-6.76(2H,m,Ar-H),6.11(1H,s,CH),5.69 (2H,s,CH2),3.75-3.54(2H,dd,CH_2),

Compound(4e)IR (KBr): 3332,3186 (NH str.), 1681,1581 (C=C), 1488 (C-N), 1334 (CH), 1280,1203,1010 (C-C), 941, 748 (CH), 694 (CH), cm-1; 1H NMR (200 MHz, DMSO-d6) δ(ppm): 10.45(1H,s, NH), 8.42-8.41(1H,d, Ar-CH) 8.31-8.29(1H,d, Ar-CH),8.11- 8.09(1H,d,Ar-CH), 7.82-7.76(3H,mAr-CH), 7.75-7.57(2H,m,Ar-CH), 7.56-7.54(1H,t,Ar-H), 7.43-7.39(2H,t,Ar-CH), 7.17-7.13(2H,t,Ar-CH), 6.21(1H,s,CH), 5.76(2H,s,CH_2), 3.76-3.55(2H,dd, CH_2)

Compound (4f); IR (KBr): 3332(NH str.),3178(Ar-CH str.), 3062,1681(>C=O, thiazolidine ring),1612,1527,1488, 1288, 1280,1203,1010, 948, 748 cm-1; 1H NMR (200 MHz, DMSO-d6) δ(ppm): 11.56 (1H,s, NH), 8.40-8.36(1H,d, Ar-CH) 8.29-8.26(2H,d, Ar-CH), 8.18-8.08(1H,d,Ar-CH), 7.94(1H,s,CH), 7.84-7.69(4H,m,Ar-CH), 7.57-7.41(4H,m,Ar-CH), 6.74-6.69(2H,m,Ar-CH), 6.13(1H,s,CH) 5.68(2H,s,CH_2), 3.71-3.56(2H,dd,CH_2), 2.97-2.94(6H, s,N(CH_3)$_2$)

RESULTS AND DISCUSSION

Formation of 4-thiazolidinone 4**a** was confirmed by IR spectroscopy, which showed the ring C=O stretching characteristic of 1,3-thiazolidine-4-ones ring in the range of ν_{max} at 1681,1710 cm^{-1}.

^{1}H-NMR spectra for **4a** showed methylene CH_2 ($COCH_2S$) protons of the 4-thiazolidinone ring between δ 3.73-3.83 ppm as the double doublet signal as they are diastereotopic protons hence couples with each other and splits the signals of each other to show doublet of doublet and singlet signal at δ 6.12 ppm for CH (SCHN). Different substituents of aromatic aldehydes were studied for the synthesis of thiazolidines by conventional heating and under microwave irradiations. Results are summarized in **table-I**.

From table-I, it is clear that the rates of the reaction were increase under the influence of microwave radiations as compared to conventional heating condition. In conventional heating method the yield is low as compared to microwave irradiation. Microwave irradiation facilitates the polarization of the molecule under irradiation causing rapid reaction to occur.

Table 1: Synthesis of Thiazolidines substituted with indolo [2,3-b] quinoxaline under conventional and microwave heating

Entry	R-	Conventional heating		Microwave heating		
		Time in Hrs.	% Yield*	Microwave power in Watt.	Time in min.	% Yield*
4a	H	10	64	450	15	74
4b	3-NO_2	10	52	450	23	67
4c	4-CH3	10	67	450	15	78
4d	2-OH	10	65	450	15	76
4e	2-Cl	10	58	450	20	72
4f	4-$N(CH_3)_2$	10	62	450	15	70

**Yields refer to pure products.*

CONCLUSION

Researchers across the globe have developed green resolution to design synthesis in the organic chemistry. The microwave assisted greener chemical transformation affords excellent product yield, reduced reaction time and minimization or elimination of by product. The result obtained confirms superiority of microwave irradiation over the conventional heating method **(Table-I).**

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