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SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL INDOLIZINE DERIVATIVES

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ABSTRACT

A novel approach has been adopted for the synthesis of Indolizine nucleus. Pyridinium-*N*-methylides (1a, b) were synthesized by reacting pyridine with different haloacetic acids. Further, the indolizine nucleus were synthesized through 1,3-cycloaddition of pyridinium-*N*-methylides with electron deficient alkynes or alkenes in presence of MnO_2 to give indolizine carboxylates (2a, b). Later on, derivatives of indolizine (4a-d) were prepared by treating 2a and 2b with hydralazine and metformin. Synthesis of indolizine 2-carboxylic acid was achieved, by reacting 2- methyl pyridine with ethylbromopyruvate. The resulting acid was treated with hydralazine and metformin to form corresponding indolizine derivatives (5a, b). Synthesized compounds were characterized by IR and NMR spectroscopic techniques.

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INTRODUCTION

Indolizine is an isomer of indole, containing 10π electrons and a fused ring system with one bridge nitrogen at the junction[1]. Indolizine is an important *N*-containing heterocyclic nucleus. It has several previous name in chemical literature such as pyrindole, pyrrocoline and pyrrole [1,2-a]pyridine[2]. The aromatic indolizine system does not appear to occur naturally, however its perhydro derivatives indolizidines represent scaffold for several alkaloids[3].

Indolizine have generated interest due to their wide biological activities such as, anticancer[4], anti-tubercular[5], antiarrythmic[6], antioxidant[7] and anti-HIV[8]. Indolizine derivatives are also reported for oral hypoglycemic agents[9].

The indolizine derivatives have been useful pharmacological properties capable of rendering in treatment of certain pathophysiological syndromes of the heart more particularly in the treatment of angina pectoris auricular and ventricular arrhythmias of various origin.

Most of the currently used agents cannot be used as single therapy because of several toxicities associated with these drugs. Sometime use of therapeutic agent alone in the treatment of disease is limited by side effects caused by its own action. Then combination of drugs with different pharmacotherapaeutic effects are feasible. Combination drug therapy can be applied either to overcome the side effects of a single drug or to add beneficial effects. The principle of combination drug therapy can be achieved by using concomitant administration of two or more single active drug or by designing the drugs in which more than one active pharmacophore are combined in one molecule[10].

General method of synthesis for Indolizine nucleus involves: 1) Condensation of 2-alkyl pyridine with acid anhydrides or α-haloketones, 2) Reactions of substituted pyridine with ester like, methyl propiolate and 3) Reactions of pyridinium *N*-methylides with ethylene in presence of an oxidant[11]. The third route is widely used for synthesis of indolizine with substitution. The present work deals with synthesis of indolizine by 1, 3-cycloaddition of Pyridinium-*N*-methylides and ester methylpropiolate/ethylpropiolate with moderate to good yields.

MATERIALS AND METHODS

Chemistry

Chemicals used for the synthesis, were purchased from Spectrochem. Solvents were re-distilled before use. Characterization of synthesized derivatives including intermediates, were done by FTIR (Bruker spectrophotometer) and, NMR (Bruker-400 spectrometer). Chemical shifts were measured in δ ppm using TMS as internal standard. TLC were performed on pre-coated silica gel plates (Merck 60 F_{254}) to check the progress of reaction as well as purity of the synthesized molecules. Melting point was checked by open capillary tube method and reported uncorrected.

General procedure for the synthesis of *N-(*carboxymethyl) pyridinium halides (1a & b):

To the solution of pyridine (100 mmol) in ethylacetate (60 mL) appropriate haloacetic acid (100 mmol) was added and the reaction mixture was refluxed for 3 h with constant stirring to get *N*-(carboxymethyl-pyridinium) halides with 80-85% yield.
N-carboxymethyl-pyridiniumchloride (1a): mp: 150-154°C. IR (cm^{-1}): 3392 (-OH str.), 2968 (>C-H, str.), 1729 (>C=O, str.)
N-carboxymethyl-pyridinium bromide (1b): mp: 176-180°C. IR (cm^{-1}): 3388 (-OH, str.), 2958 (>C-H, str.), 1719 (>C=O, str.).

General procedure for synthesis of Indolizine (2a-b):

A suspension of *N*-(carboxymethyl)-pyridinium halide (**1a/1b** 10 mmol), methylpropiolate (50 mmol) and trimethylamine (1.5 mL) in toluene (80 mL) was stirred at 90° C for 3 h. Completion of reaction was monitored by TLC. Cooled the reaction mixture at room temperature, filtered and washed the residue with acetone. Combined the filtrates and removed the solvent under reduced pressure. Residue obtained so, was purified by column chromatography using petroleum ether and ethyl acetate as eluent (9:1) to afford product in 60-70 % yield.

Methylindolizine-1-carboxylate (2a): brown oil, IR (cm^{-1}): 3114 (>CH-, str.), 1694 (>C=O, str.) ^{1}H NMR (400 MHZ, CDCl3): δ = 8.14 (d, 1H), 7.93 (d, 1H), 7.20 (d, 1H), 7.17 (d, 1H), 6.99 (m, 1H), 3.10 (3H, CH_3).

Ethylindolizine-1-carboxylate (2b): pale yellow oil. IR (cm^{-1}): 3214 (>C-H, str.), 1676 (>CO, str.)
^{1}H NMR (400 MHZ, CDCl3): δ = 8.17 (d, 1H), 7.98 (d, 1H), 7.23 (d, 2H), 7.03 (t, 1H), 6.68 (t, 1H), 4.37 (q, 2H), 1.39 (t, 3H).

General procedure for the synthesis of indolizine 2- carboxylic acid (3a):

Procedure: A solution of ethylbromopyruvate (35 mmol) and α- picoline (25 mmol) in dry ethanol (20 mL) was refluxed on water bath for 4 h and kept at room temperature for 3 days. Excess of ethanol was removed under reduced pressure; the residue obtained so, was dissolved in water and extracted with chloroform to remove colored impurities. Solution was made alkaline with aqueous sodium hydrogen carbonate solution and extracted with ether. To the aqueous part excess of sodium hydrogen carbonate was added and the mixture was heated on the steam bath for 4 h followed by addition of dilute hydrochloric acid to get a grey colored mass. Filtered the solid and re-crystallized from absolute ethanol with 30% yield[12].
Indolizine 2-carboxylic acid (3a): mp: 220 °C IR (cm^{-1}): 3429 (-OH, str.), 3130 (>C-H, str.) , 1672 (>C=O, str.)
^{1}H NMR (400 MHZ,$CDCl_3$): δ = 12.6 (s, 1H), 8.25 (d, 1H), 7.99 (s, 1H), 7.43 (d, 1H), 6.74 (m, 2H), 6.62 (t, 1H).

Synthesis of *N*-(pthalizin-4ylmethyl)-indolizine1-carbohydrazide (4a & b):

A mixture of compound 2a-b (1 mmol) and hydralazine (1 mmol) in absolute ethanol (50 mL) as refluxed for 4 h. The completion of reaction was monitored by TLC. Cooled the mixture and then poured into ice cold water. The solid obtained was filtered off and re-crystallized from absolute ethanol to give 4a & 4b.[13,14]

N-(pthalizin-4ylmethl)-indolizine1-carbohydrazide (4a): mp: 125°C. IR (cm^{-1}): 3151 (-NH, str.), 2985 (>C-H, str), 1655 (>C=O), ^{1}H NMR (400 MHZ, CDCl3): δ= 11.78 (s, 1H), 9.14 (m, 3H), 8.56 (m, 2H), 8.25 (d, 1H), 8.09 (t, 1H), 7.95 (t, 1H), 7.56 (d, 2H), 7.28 (m, 2H).

2-imino-2-(2-(indolizine-1-carbonyl)hydrazinyl)-N, N-dimethylacetamide(4b):mp: 135 °C. IR(cm^1): 3121 (NH, str), 2995 (>CH, str), 1665 (>C=O), ^{1}H NMR (400 MHZ,$CDCl_3$):δ=11.56.(s,1H),8.76(s,1H),8.17(m,2H),8.65(m,2H),7.61(m,1H),7.43(t,1H),7.56(m,3H),1.97(s,6H).

Synthesis of 2-imino-2(2-(indolizine-1-carbonyl) hydrazinyl)-*N*,*N*-dimethylacetimidamide (4c-d)

A mixture of compound 2a-b (1 mmol) and metformin (1 mmol) in absolute ethanol (50 mL) was refluxed for 4 h and monitored by TLC. Cooled the mixture and poured into ice cold water. The solid obtained was filtered off and crystallized from ethanol to give compound 4c, 4d.

N-(pthalizin-4ylmethl)-indolizine1-carbohydrazide (4c): mp:155 °C. ^{1}H NMR (400 MHZ, DMSO-d_6): δ = 11.68 (s, 1H), 9.31 (m, 3H), 8.56 (m, 2H), 8.21 (d, 1H), 8.09 (t, 1H), 7.56 (t, 1H), 7.36 (d, 2H), 7.28 (m, 2H).

2-imino-2(2-(indolizine-1-carbonyl)hydrazinyl)-N,N-dimethylacetimidamide(4d): mp: 115 °C. IR(cm^{-1})3361(-NH, str), 3062(>CH, str),1361(CN,str), ^{1}H NMR (400 MHZ,$CDCl_3$): δ= 11.50(s, 1H),8.75(s, 1H), 8.15(m, 2H), 8.02(m, 2H),7.51(m, 1H),7.11(m, 3H),1.85(s, 6H).

Synthesis of *N*-(pthalazin-1-yl) indolizine-2-carbohydrazide (5a):

Procedure: Indolizine 2-carboxylic acid (3) (0.5 mmol), HATU (0.75 mmol) and DIPEA (3 mmol) in dichloromethane was added, and the solution was stirred at 0-10 °C for 20 minutes, then hydralazine (0.55 mmol) is added, mixture is stirred at room temperature for 3 h.The solvent was removed and residue was extracted with dichloromethane/methanol. Combined organic layer solvent evaporated under reduced pressure then residue was purified by column chromatography eluting with Dichloromethane/methanol.[15]

N-(pthalzin-1-yl) indolizine-2-carboxamide (5a): mp:220 °C IR(cm^{-1}) 3313(-NH, str), 2919(>CH, str), 1646(>CO, str), ^{1}H NMR (400 MHZ,$CDCl_3$): δ= 10.91(s,1H), 8.66(s,1H),7.93(d,1H),7.85(d,2H),7.44(m,1H),7.11(d,1H),6.88(d,2H),6.41(m,2H),6.17(s, 1H),4.1(s,1H).

Synthesis of *N*-(*N*-(*N*,*N*-dimethylcarbamimidoyl)carbamimidoyl)indolizine-2-carboxamide (5b):

Procedure: Indolizine 2-carboxylic acid **(3a)** (0.5 mmol), HATU (0.75 mmol) and DIPEA (3 mmol) in dichloromethane was added, and the solution was stirred at 0-10 °C for 20 minutes, then the metformin (0.55 mmol) mixture is stirred at room temperature for 3 h.The solvent was removed and residue was extracted with dichloromethane/methanol. Combined organic layer solvent evaporated under reduced pressure and residue was purified by column chromatography eluting with Dichloromethane/methanol.

N-(*N*-(*N*,*N*-dimethylcarbamimidoyl)carbamimidoyl)indolizine-2-carboxamide (5b): mp:180 °C IR(cm^{-1}) 3123(-NH, str), 2890(>CH, str),1631(>CO, str), ^{1}H NMR (400 MHZ,$CDCl_3$):δ=11.91(s,1H),8.51(s,1H),7.44(d,1H),7.11(d,2H),6.83(m,1H),6.41(d,1H),6.21(d,2H),6.06(m,1H),3.32(s,6H).

RESULTS AND DISCUSSION:

We have carried out synthesis of substituted indolizine-1- carboxylates by using pyridine and haloacetic acid in presence of ethylacetate as solvent to form pyridinium salt (1a) which is recrystallized from methanol. This salt is reacted with methyl propiolate to form the substituted indolizine(2a). Substituted indolizines have been prepared by treating with methylpropiolate/ethylpropiolate in presence of triethylamine and toluene as solvent. The products were purified by column chromatography using 60-120 mesh silica gel using hexane-ethylacetate as solvent and the yield was found to be 60-70%.

The structure of substituted indolizine was confirmed on the basis of sharp singlet at δ 3.10 corresponding to the $COOCH_3$ protons. This was then reacted with hydralazine to give the target molecule (4a). This structure was confirmed on the basis of characteristic peak at δ 11.78 for CONH protons.

Indolizine 2- acid (3a) is also synthesized by reacting picoline with ethylbrompyruvate this structure was confirmed by a sharp singlet at δ 12.6 for COOH proton. This acid was treated with hydralazine and metformin to form the amide derivatives (5a). This amide derivatives was confirmed by presence of NH group was observed at δ 10.91. Remaining all protons was seen in the ^{1}H NMR spectrum with expected chemical shifts and integral values.

CONCLUSION

Current study reveals the synthesis of 1- substituted indolizines from pyridinium halides in presence of MnO_2 and commercially available alkyne which serve as dipolarophiles gives the products in moderate to good yields. Derivatives are prepared by reacting with hydralazine and metformin. Indolizine 2-acid is synthesized by using picoline with ethylbromopyruvate and it is treated with hydralazine and metformin to form the corresponding derivatives.co drugs of indolizine is synthesized and it is evaluated for the hydrolysis study in our future study from which bioavailability of drugs can be studied and also in vivo animal study can be conducted for antihypertensive and antidiabetic activity.

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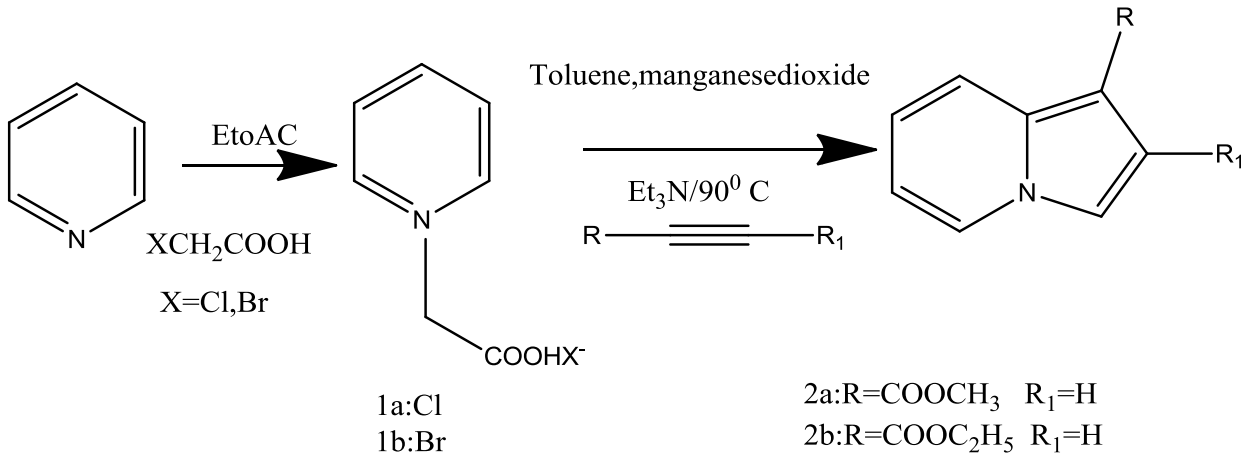
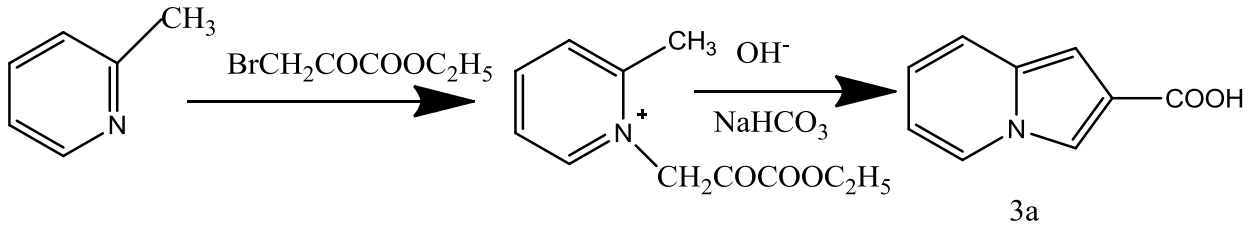
Conflict of interest- The authors declare that they have no competing interest.

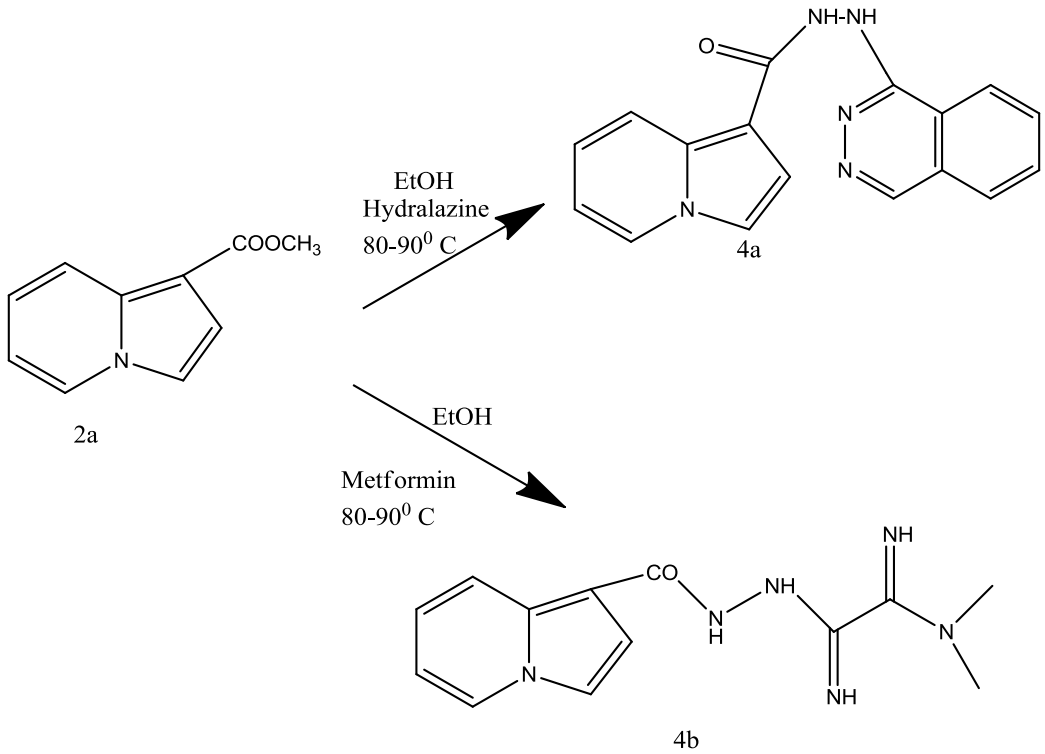


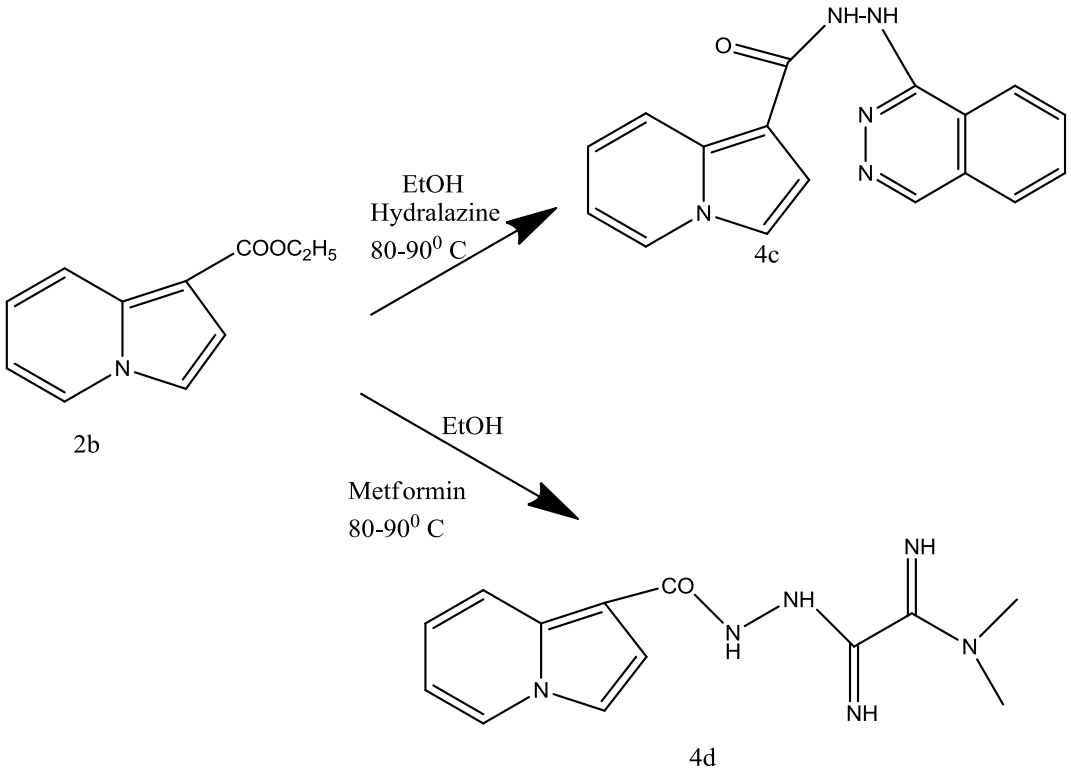
Scheme-I: Step-1: Formation of pyridinium salt (1a-b)

Step:2 Formation of substituted indolizine (2a-b).

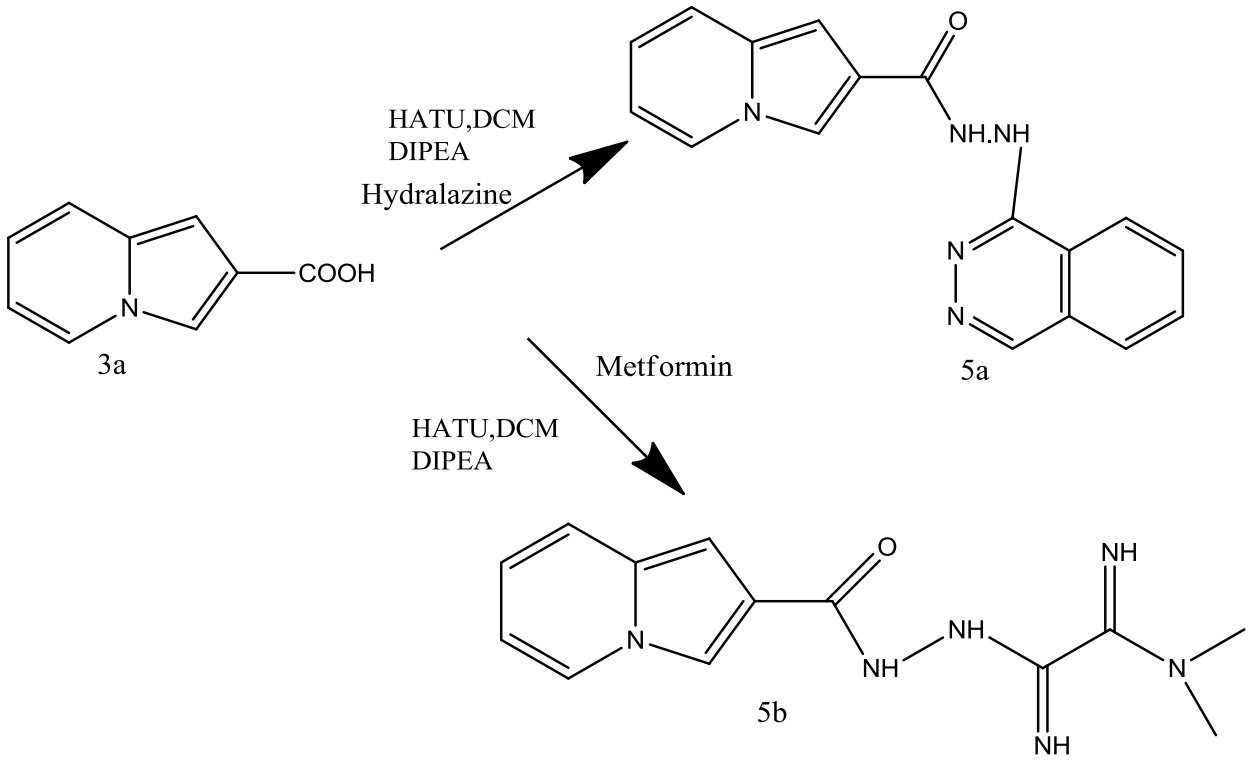


Scheme-II: Synthesis of indolizine 2-carboxylic acid (3a).





Scheme-III: Derivatives of indolizine 1-carboxylate (4a-d).



Scheme-IV: Derivatives of indolizine-2-carboxylic acid (5a & b).

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