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Synthesis of Diazepine and Thiazepine derivatives of 1H-imidazo [4, 5-b] pyridines

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Abstract
Benzodiazepines and Benzothiazepines are seven membered nitrogen containing heterocyclic compounds. These are important drugs possessing various biological activities. These are widely used as anticonvulsant, antianxiety, sedative, antidepressive, hypnotic and neuroleptic agents. In the present study, a novel series of 2-(4-substituted phenyl)-4-(1H-imidazo[4,5-b]pyridin-2-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepines and 2-(4-substituted phenyl)-4-(1H-imidazo[4,5-b]pyridin-2-yl)-2,3-dihydrobenzo[b][1,4]thiazepines were synthesized and screened for their antimicrobial activity.

Keywords
Anticonvulsant, Sedative, Neuroleptic agents, Antidepressants, Antianxiety.

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INTRODUCTION:
Heterocyclic compounds are often considered privileged structures in medicinal chemistry due to their biological effects. Benzodiazepines are one of the important class of therapeutic agents for example various benzodiazepines have anticonvulsants, antihypnotic and anxiolytic activities. Benzodiazepines serve as cholecystokinin A and B antagonists, HIV trans-activator antagonists and HIV reverse transcriptase inhibitors. Due to this importance, a novel series of diazepines and thiazepines were synthesised.

MATERIALS AND METHODS:
All melting points were taken in open capillaries on a Veego VMP-1 apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin-Elmer FT IR 240-c spectrometer. The ^{1}H NMR spectra were recorded on Varian-Gemini 200 MHz spectrometer in DMSO-d6 using TMS as an internal standard and mass spectra were recorded on Schimadzu QP 5050A spectrometer.

EXPERIMENTAL SECTION
A. Synthesis of 2-(4-substituted phenyl)-4-(1*H*-imidazo[4,5-*b*] pyridin-2-yl)-2,3-dihydro-1*H*-benzo [*b*][1,4] diazepines
i)**Synthesis of 1-(1*H*-imidazo[4,5-*b*] pyridin-2-yl) ethanone (XV)**
Potassium dichromate (0.069 mol) and water (35 ml) were mixed with constant mechanical stirring in a 3-necked flask fitted with a condenser and an addition funnel. The corresponding 1-(1H-imidazo[4,5-b] pyridin-2-yl) ethanol **(3)** (0.13 mol) was gradually added to the cooled stirring solution and stirring was continued for another 10 minutes. A cooled solution of H2SO4 (30 ml) and water (18ml) was then added drop wise over a period of 1 hr., after which water (100 ml) was introduced into the reaction mixture. The mixture was extracted with dichloromethane (3 x 150 ml), followed by subsequent washing with water (200 ml) and 5% sodium carbonate (200 ml). The separated organic layer was dried over anhydrous sodium sulfate, filtered and the solvent vanished *in vacuo*. The solid obtained was distilled and recrystallized from EtOH.

ii) Synthesis of 3-(4-chlorophenyl)-1-(1*H*-imidazo [4,5-*b*] pyridin-2-yl)prop-2-en-1-one (XVIc).

1-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)ethanone (XV, 0.01mol) was condensed with 4-chlorobenzaldehyde (0.015 mol) by refluxing in 20ml of absolute alcohol and NaOH solution for 5hrs the reaction mixture was cooled and neutralized with HCl.

The precipitate formed was filtered and passed through silica gel column and the product was eluted from 60% ethylacetate andhexane. These compounds were characterized by their spectral data.

Other compounds (XVIa-i) in this series were prepared similarly and their characterization data were recorded in **Table 5.**

iii) Synthesis of 2-(4-chlorophenyl)-4-(1*H*-imidazo [4,5-*b*]pyridin-2-yl)-2,3-dihydro-1*H*-benzo [*b*][1,4] diazepine (XVII)

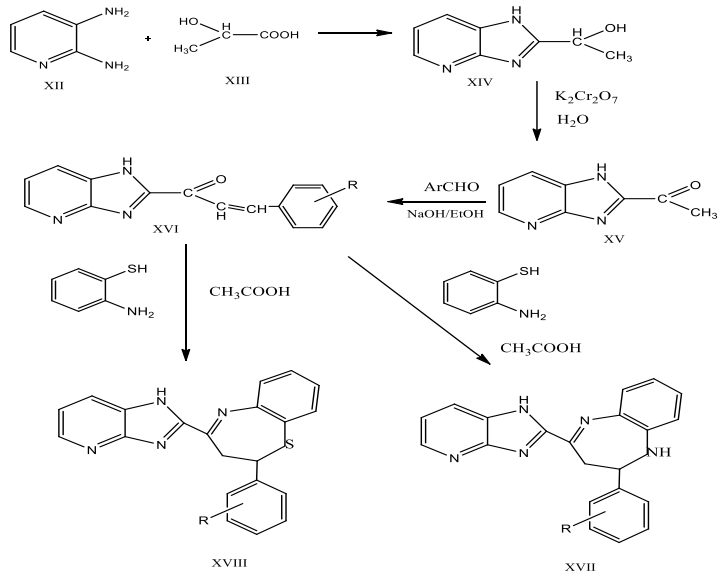
3-(4-chlorophenyl)-1-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)prop-2-en-1-ones (XVIc 0.1 mol) was added to benzene-1,2-diamine (0.1 mol) dissolved in toluene (25 ml). To the mixture was added few drops of acetic acid as a catalyst. The mixture was refluxed for 5-6 h and the reaction monitored using TLC. The solution was left to cool to room temperature and the excess solvent was removed on a rotary evaporator. The resulting solid was filtered, dried and recrystallized from ethanol.

Other compounds (XVIIa-i) in this series were prepared similarly and their characterization data were recorded in **Table 6.**

B.2-(4-substitutedphenyl)-4-(1*H*-imidazo[4,5-*b*] pyridine-2-yl)-2,3-dihydro benzo[*b*][1,4]thiazepines (XVIII)

i)Synthesis of 2-(4-chlorophenyl)-4-(1*H*-imidazo [4,5-*b*]pyridin-2-yl)-2,3-dihydrobenzo[*b*][1,4] thiazepines (XVIIIc).

3-(4-chloro phenyl)-1-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)prop-2-en-1-ones (XVI 0.1 mol) was added to 2-aminobenzenethiol (0.1 mol) dissolved in toluene (25 ml). To the mixture was added few drops of acetic acid as a catalyst. The mixture was refluxed for 5-6 h and the reaction monitored using TLC. The solution was left to cool to room temperature and the excess solvent was removed on a rotary evaporator. The resulting solid was filtered, dried and recrystallized from ethanol.



XVII & XVIII, R=

a) H
b) -2 OH
c) -4 Cl
d) -4 Br
e) -4 NO_2
f) -4 CH_3
g) -4 OCH_3
h) -3 OCH_3 , -4 OH
i) -4 OH

SCHEME-3

SPECTRAL DATA.

IR Spectrum data of compound XV:

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm-1) at: 3450 (NH), 3146 (C-H, Aromatic), 1708 (C=O), 1528 (C=N).

1 H NMR Spectrum data of compound XV:

PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (□□ppm) at:12.9(s,1H,NH), 8.2(d, 1H,ArH), 7.8(dd,1H,ArH), 7.4(s,1H,ArH), 1.3(s,3H,CH3).

IR Spectrum data of compound XVIc:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm-1) at: 3364 (N-H), 3150 (C-H, Aromatic), 1683 (C=O), 1615 (C=C), 1576 (C=N), 765(C-Cl).

1 H NMR Spectrum data of compound XVIc:
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (ppm) at:13.1(s,1H,NH, imidazole ring), 8.1(d,1H,ArH,), 7.7(d,1H,ArH), 7.4(d,1H,ArH), 7.2 (d, 2H, ArH), 6.9(m, 2H, ArH), 6.4(d, 1H, CH), 6.2(d, 1H,CH).

IR Spectrum data of compound XVIIc:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm-1) at: 3256 (N-H), 3133(N-H), 2901 (C-H, Aromatic), 1602 (C=N),1592 (C=C), 647(C-Cl).

1 H NMR Spectrum data of compound XVIIc:
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (ppm) at:13.3(s,1H,NH, imidazole ring), 8.5(d,1H,ArH, pyridine ring), 8.2(d,2H,ArH, pyridine ring), 7.9(d,1H,ArH), 7.6 (d, 2H, ArH), 7.2(t, 2H, ArH), 7.0(d, 1H, ArH), 6.8(d, 1H, ArH), 6.7(t, 1H, ArH), 4.0(s, 1H, ,NH (Benzodiazepine ring), 3.5(d, 2H, CH2), 3.0(t, 1H, CH).

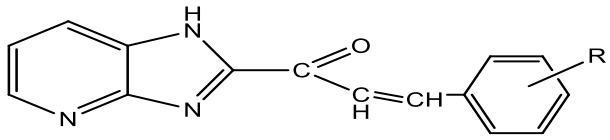
Mass Spectrum data of compound XVIIc:
ESI: *m/z* 374 [M+H]+.

IR Spectrum data of compound XVIIIc:
The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm-1) at: 3364(N-H), 2994 (C-H, Aromatic), 1596 (C=N),1580 (C=C), 700(C-S).

1 H NMR Spectrum data of compound XVIIIc:
PMR spectrum (DMSO-d6) of the compound has been found to exhibit proton signals (ppm) at:13.1(s,1H,NH, imidazole ring), 8.4(d,1H,ArH, pyridine ring), 7.9 (d,2H,ArH, pyridine ring), 7.6(d,1H,ArH), 7.3 (m, 4H, ArH), 6.9(t, 1H, ArH), 6.6(t, 1H, ArH), 6.3(s, 1H, Ar-H), 5.9(d,1H ArH), 3.8(d,2H, CH2), 3.3(t, 1H, CH).

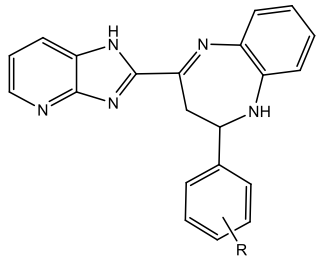
Mass Spectrum data of compound XVIIc:
ESI: *m/z* 390 [M+H]+

Table 5 – Physical data of 3-(4-substituted phenyl)-1-(1H-imidazo[4,5-b]pyridine-2-yl)prop-2-en-1-one(XVI)



S.No	Compound	R	Chemical Formula	M.P(^{0}C)	Yield (%)	Elemental Analysis Found (Calc %)		
						C	H	N
1	XVI a	H	$C_{15}H_{11}N_3O$	248-250	65	72.32 (72.28)	4.40 (4.45)	16.85 (16.86)
2	XVI b	-2-OH	$C_{15}H_{11}N_3O_2$	254-256	62	67.95 (67.92)	4.19 (4.18)	15.85 (15.84)
3	XVI c	-4 Cl	$C_{15}H_{10}ClN_3O$	268-270	64	63.56 (63.50)	3.52 (3.55)	14.80 (14.81)
4	XVI d	-4 Br	$C_{15}H_{10}BrN_3O$	299-301	58	54.92 (54.90)	3.05 (3.07)	12.87 (12.80)
5	XVI e	-4 NO_2	$C_{15}H_{10}N_4O_3$	290-292	49	61.20 (61.22)	3.48 (3.43)	19.06 (19.04)
6	XVI f	-4 CH_3	$C_{16}H_{13}N_3O$	218-220	62	72.98 (72.99)	5.01 (4.98)	16.02 (15.96)
7	XVI g	-4 OCH_3	$C_{16}H_{13}N_3O_2$	228-230	61	68.84 (68.81)	4.66 (4.69)	15.08 (15.05)
8	XVI h	-3 OCH_3 -4 OH	$C_{16}H_{13}N_3O_3$	210-212	65	65.10 (65.08)	4.40 (4.44)	14.25 (14.23)
9	XVI i	-4 OH	$C_{15}H_{11}N_3O_2$	260-262	62	67.95 (67.92)	4.19 (4.18)	15.88 (15.84)

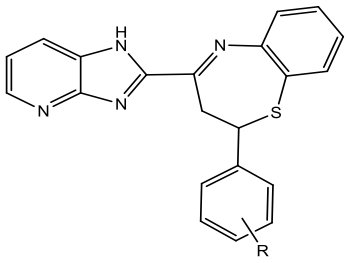
Table 6 – Physical data of 2-(4-substituted phenyl)-4-(1H-imidazo[4,5-b] pyridin-2-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepines (XVII)



XVII

S.No	Compound	R	Chemical Formula	M.P(^{0}C)	Yield (%)	Elemental Analysis Found (Calc %)		
						C	H	N
1	XVII a	H	$C_{21}H_{17}N_5$	228-230	48	74.35 (74.32)	5.01 (5.05)	20.66 (20.63)
2	XVII b	-2-OH	$C_{21}H_{17}N_5O$	265-267	52	70.99 (70.97)	4.85 (4.82)	19.79 (19.71)
3	XVII c	-4 Cl	$C_{21}H_{16}ClN_5$	280-282	56	67.45 (67.47)	4.33 (4.31)	18.77 (18.73)
4	XVII d	-4 Br	$C_{21}H_{16}BrN_5$	250-252	56	60.35 (60.30)	3.88 (3.86)	16.76 (16.74)
5	XVII e	-4 NO_2	$C_{21}H_{16}N_6O_2$	275-277	58	65.60 (65.62)	4.25 (4.20)	21.89 (21.86)
6	XVII f	-4 CH_3	$C_{22}H_{19}N_5$	245-247	54	74.80 (74.77)	5.45 (5.42)	19.80 (19.82)
7	XVII g	-4 OCH_3	$C_{22}H_{19}N_5O$	258-260	62	71.55 (71.53)	5.20 (5.18)	18.95 (18.96)
8	XVII h	-3 OCH_3 -4 OH	$C_{22}H_{19}N_5O_2$	223-225	64	68.60 (68.56)	4.95 (4.97)	18.15 (18.17)
9	XVII i	-4 OH	$C_{21}H_{17}N_5O$	281-283	65	70.95 (70.97)	4.80 (4.82)	19.70 (19.71)

Table 7 – Physical data of 2-(4-substituted phenyl)-4-(1H-imidazo[4,5-b] pyridin-2-yl)-2,3-dihydro-1H-benzo[b][1,4]thiazepine (XVIII)



XVIII

S.No	Compound	R	Chemical Formula	M.P(^{0}C)	Yield (%)	Elemental Analysis Found (Calc %)		
						C	H	N
1	XVIII a	H	$C_{21}H_{16}N_4S$	235-237	45	70.78 (70.76)	4.50 (4.52)	15.70 (15.72)
2	XVIII b	-2-OH	$C_{21}H_{16}N_4OS$	272-274	52	67.78 (67.72)	4.35 (4.33)	15.01 (15.04)
3	XVIII c	-4 Cl	$C_{21}H_{15}ClN_4S$	260-262	52	64.50 (64.53)	3.81 (3.87)	14.36 (14.33)
4	XVIII d	-4 Br	$C_{21}H_{15}BrN_4S$	255-257	53	57.98	3.44	12.85

						(57.94)	(3.47)	(12.87)
5	XVIII e	-4 NO_2	$C_{21}H_{15}N_5O_2S$	285-287	52	62.80 (62.83)	3.81 (3.77)	17.44 (17.45)
6	XVIII f	-4 CH_3	$C_{22}H_{18}N_4S$	264-266	58	71.35 (71.32)	4.95 (4.90)	15.10 (15.12)
7	XVIII g	-4 OCH_3	$C_{22}H_{18}N_4OS$	242-244	54	68.38 (68.37)	4.72 (4.69)	14.55 (14.50)
8	XVIII h	-3 OCH_3 -4 OH	$C_{22}H_{18}N_4O_2S$	268-270	55	65.60 (65.65)	4.52 (4.51)	13.90 (13.92)
9	XVIII i	-4 OH	$C_{21}H_{16}N_4OS$	290-292	57	67.70 (67.72)	4.30 (4.33)	15.06 (15.04)

RESULTS AND DISCUSSION:

The compound 2,3-diaminopyridine (XII) on treatment with 2-hydroxy-propanoic acid (XIII) gives 1*H*-imidazo[4,5-*b*] pyridin-2-hydroxy-ethane (XIV). Compound (XIV) on gradual addition to Potassium dichromate and water mixture during stirring followed by drop wise addition of H2SO4 and water over a period of 1hr produced 1-(1H-imidazo[4,5-b]pyridin-2-yl) ethanone (XV). The compound 1-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)ethanone (XV) on reflux condensation with various aromatic aldehydes in absolute alcohol followed by neutralization with alkali afforded 3-(4-substitutedphenyl)-1-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)prop-2-en-1-ones (XVI) in excellent yields.

Finally the compound 3-(4-substitutedphenyl)-1-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)prop-2-en-1-ones (XVI) on treatment with benzene-1,2-diamine in presence of acetic acid resulted in the formation of 2-(4-substituted phenyl)-4-(1*H*-imidazo[4,5-*b*] pyridin-2-yl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepines(XVII).

Compound (XVI) on reaction with 2-aminobenzenethiol produced 2-(4-substitutedphenyl)-4-(1*H*-imidazo[4,5-*b*] pyridin-2-yl)-2,3-dihydrobenz o[b][1,4] thiazepines (XVIII) in good yields **(Scheme-3)**

(Table 5-7). The structures of the products XV to XVIII have been established on the basis of analytical and spectral data.

Twenty seven new compounds have been synthesized in **Scheme-3.**

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