Synthesis of novel derivatives of 4-Pyridine carboxylic acid hydrazide and their activity on central nervous system

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Abstract: Six novel derivatives (2-7) of 4-Pyridine carboxylic acid hydrazide (PCH) were synthesized by treating this lead molecule with substituted arylsulphonyl and benzoyl chlorides. The molecular structures of the newly derived products were characterized by the help of UV Visible, IR, FAB, ^{1}HNMR spectroscopy and CHN analysis. During the preliminary pharmacological screening, it was observed that the synthesized compounds induced noticeable changes on motor activity of the animals. Interesting structure activity relationship was also observed among the synthesized molecules. Because of the interesting affect on motor activity, the newly synthesized derivatives can further be evaluated for their effects on CNS.

Keywords: 4-Pyridine carboxylic acid hydrazide, Sulphonyl and benzoyl chloride, Pharmacological screening.

INTRODUCTION

4-PCH has gained wide application in the field of medicinal chemistry as Isoniazid (Brennan PJ and Young DB, 2008; Chambers HF and Deck HD, 2009). Several of the studies have reported its analogues with diversified biological activities. Researchers have shown the potential of PCH derivatives for central nervous system (Thomas *et al*., 2011; Tripathi *et al*., 2011). The activity has also been reported for cardiovascular system (Prikhod'ko *et al*., 1977) and gastro-intestinal tract (Hussain, 2009).

From the literature study (Haug*et al*., 2002; de Oliveira *et al*., 2011; de Oliveira *et al*., 2012; Khattab, 2005; Agababyan *et al*., 2005), it has also been noticed that the molecules containing sulphonyl and benzoyl moieties possess various biological and pharmacological activities.

Keeping this in consideration, herein we have synthesized six new derivatives of 4-PCHand attempted to investigate their pharmacological effects by subjecting them to general screening protocol.

MATERIALS AND METHODS

4-PCH and all the reagents were purchased form Sigma Aldrich, London. Analytical grade solvents acetone, ethanol and hexane were obtained from E. Merck. All the solvents were distilled prior to use to ensure extra purity.

The reaction response was observed on Thin Layer Chromatography (TLC) plates of E Merck's pre-coated silica gel GF-254. Melting points of the compounds were determined with the help of Gallenkamp melting point apparatus. Ultraviolet (UV) spectra were recorded in methanol on THERMOELECTRON VISION pro V4.10. Infra red (IR) spectra were determined using KBr discs on a VECTOR$_{22}$ spectrophotometer. Mass spectra were recorded with the help of Massen Spectrophotometer MAT 331A Varian Bermen Spectrophotometer. Proton Nuclear Magnetic Resonance Spectra (^{1}HNMR) were recorded in d_6-DMSO on AVANCE 400-B spectro-photometer.

For behavioral studies, male and female albino mice (weight 20-30g) were purchased from Agha Khan University, Karachi and housed for about three days in cages under same environmental conditions with free access to water and diet.

The study was performed according to the guidelines provided by Committee on Animal Research and Ethics (CARE)(https://www.apa.org/science/leadership/care/care-animal-guidelines.pdf)

General procedure for the synthesis of 2-7

An equimolar mixture (3.6×10^{-3}M) of PCH-1 and substituted arylsulphonyl and benzoyl chlorides dissolved in acetone, continuously stirred at the ambient conditions (20-30°C) for 6-8hrs (Scheme 1-2). The reaction response was monitored with the help of TLC plates using a solvent system of EtOH: Hexane. The obtained precipitates were filtered and washed with acetone while ethanol is used for recrystallization. The precipitates were then dried in a vacuum desicator.

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Pharmacological Screening

Test compounds 2-6 (dissolved in Water for Injection) were injected intraperitoneally whereas test compound **7** (suspended in tragacanth) administered orally in the doses of 25mg/kg body weight to the test groups. Control group receiving only vehicle always run parallel to the compound treated animals.

The study was based on the examination of the CNS Stimulating activity, CNS Depressant activity, CVS, eye/ear effects and general observations qualitatively. In this concern, the animals were observed according to the provided guidelines (Turner, 1965) and their response was recorded in a Pharmacological Screening Chart (Miranda, 1986).

RESULT

Physical data of the six novel derivatives is presented in table 1. Qualitative results of pharmacological screening are shown in table 2 and 3.The synthesized compounds are characterized by UV/Visible, IR, Mass and ^{1}H-NMR spectroscopy. UV spectra of all the synthesized compounds displayed two characteristic absorbance peaks, indicating the presence of two chromophores: pyridine and phenyl ring. Further characterization of the derivatives is given as under

N -[(4-methylbenzene)sulfonyl]pyridine-4-carbohydrazide2

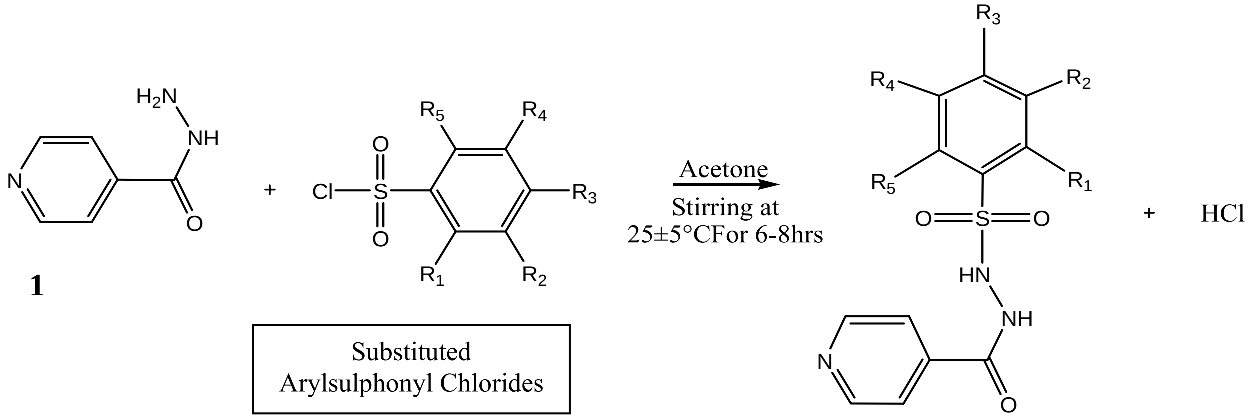
IR (cm^{-1}): 3466.0 (NH str., amine), 3117.0 (NH str., amide), 1686.9 (CO str., nicotinyl), 1631.5 (C=C str., skeletal phenyl nucleus), 3043.3 (C-H str., aromatic), 2971.0, 2811.6 (CH_3 str., aromatic), Mass: m/z 292 $[M + H]^+$, ^{1}H NMR: (400 MHz, d_6-DMSO) δ ppm: 8.883-8.899 (d, 2H, CH of C_2 and C_6 of pyridine ring; J= 6.4), 8.012-8.058 (m, 3H, NH proton of N, CH of C_3 and C_5 of pyridine ring), 7.796-7.898 (m, 4H, CH of phenyl ring), 2.158 (s, 3H, CH_3), 2.045-2.074 (d, 1H, NH of N□; J = 11.6), CHN analysis: C 53.60, H 4.50, N 14.42, O 16.48, S 11.01

N -[(2,4,6-trimethylbenzene)sulfonyl]pyridine-4-carbohydrazide 3

IR (cm-1): 3433.8 (NH str., amine), 3111.0 (NH str., amide), 1679.1 (CO str., nicotinyl), 1632.2 (C=C str., skeletal phenyl nucleus), 3043.2 (C-H str., aromatic), 2967.8, 2814.7 (CH3 str., aromatic), Mass: m/z 319 $[M]^+$, ^{1}H NMR: (400 MHz, d_6-DMSO) δ ppm: 8.891-8.906 (d, 2H, CH of C_2 and C_6 of pyridine ring; J= 6), 7.454-8.073 (m, 5H, NH proton of N, CH of C_3 and C_5 of pyridine ring, CH of phenyl ring), 2.276 (s, 9H, CH_3), 2.045-2.074 (d, 1H, NH proton of N□; J = 11.6), CHN analysis: C 56.41, H 5.37, N 13. 16, O 15.03, S10.04

N -[(4-bromobenzene)sulfonyl]pyridine-4-carbohydrazide 4

IR (cm-1): 3455.9 (NH str., amine), 3104.7 (NH str., amide), 1672.5 (CO str., nicotinyl), 1637.3 (C=C str., skeletal phenyl nucleus), 3038.6 (C-H str., aromatic), Mass: m/z 356$[M+H]^+$, ^{1}H NMR: (400 MHz, d_6-DMSO) δ ppm: 8.877-8.893 (d, 2H, CH of C_2 and C_6 of pyridine ring; J = 6.4), 7.511-8.045 (m, 7H, NH proton of N, CH of C_3 and C_5 of pyridine ring, CH of phenyl ring), 2.043-2.075 (d, 1H, NH proton of N□; J = 12.8), CHN analysis: C 40.46, H 2.83, Br 22.43, N 11.80, O 13.48, S 9.00

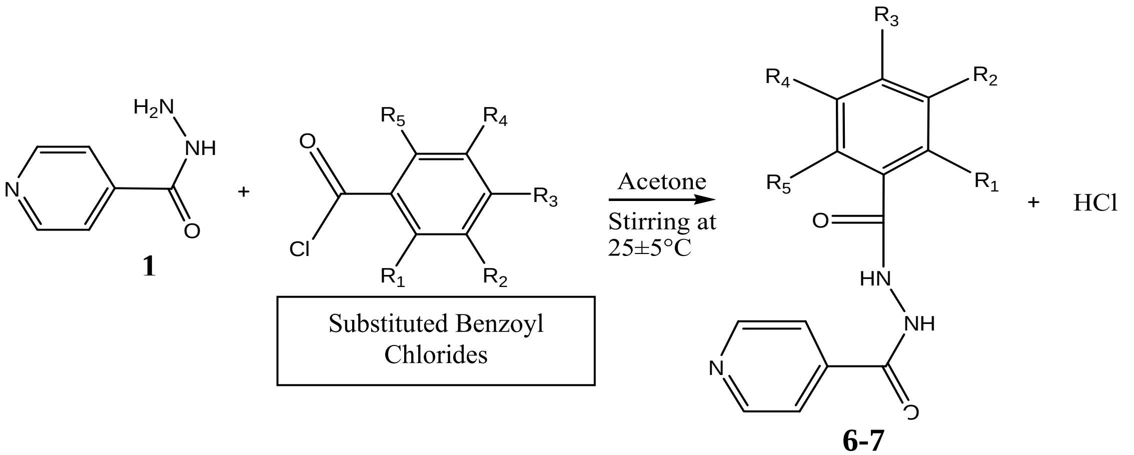


1

2-5

2 = R_1, R_2, R_4, R_5 = H, R_3 = CH_3
3 = R_2, R_4= H, R_1, R_3, R_5 = CH_3
4 = R_1, R_2, R_4, R_5 = H, R_3 = Br
5 = R_1, R_2, R_4, R_5 = H, R_3 = NO_2

Scheme 1: N□-Arylsulphonyl derivatives of 4-pyridine carboxylic acid hydrazide



6 = R$_1$, R$_2$, R4, R$_5$ = H, R$_3$ = CH$_3$
7 = R$_1$, R$_3$, R$_5$ = H, R$_2$, R4= NO$_2$

Scheme 2: N□-benzoyl derivatives of 4-pyridine carboxylic acid hydrazide

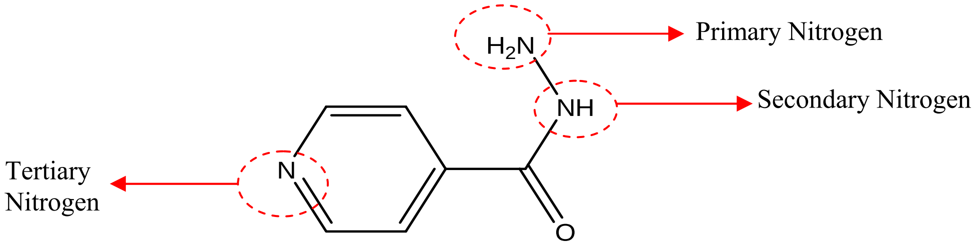


Fig. 1: Nitrogen of 4-PCH

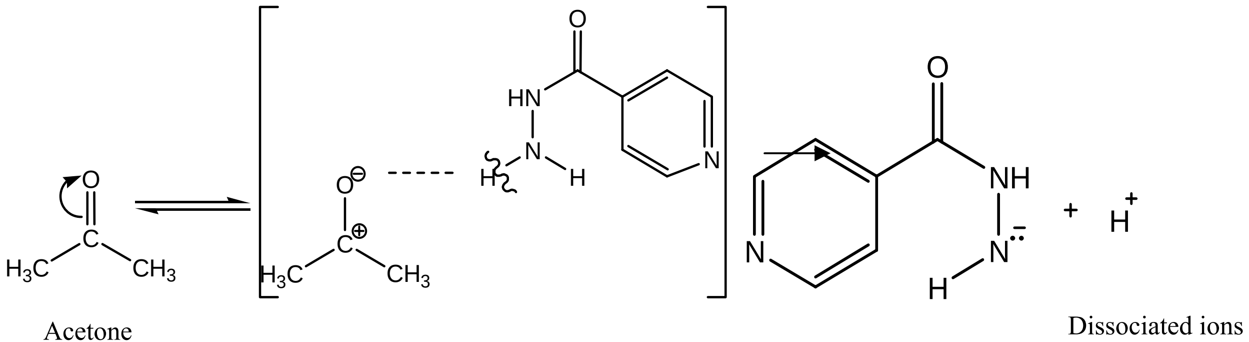


Fig. 2: Role of solvent

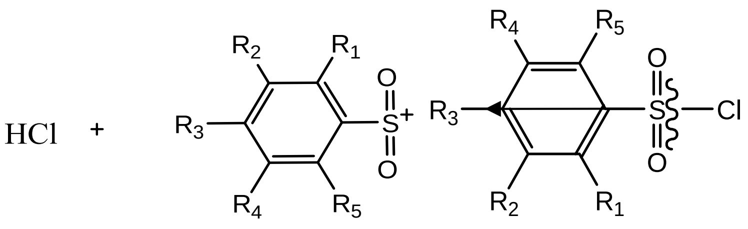


Fig. 3: Formation of HCl

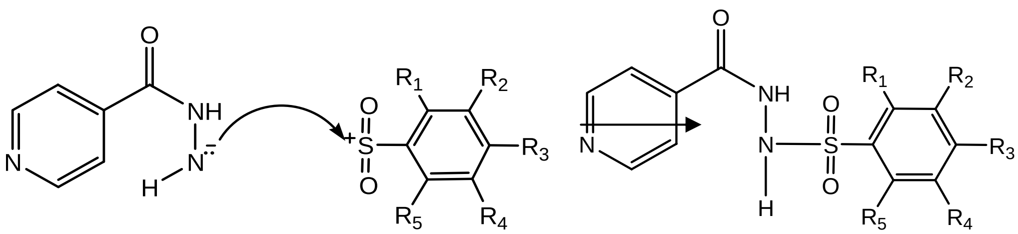


Fig. 4: Formation of Product

Scheme 3: Course of synthetic reaction for sulphonyl chlorides derivatives

Table 1: Physical characteristics of the synthesized compounds 2-7

compound	R_1	R_2	R_3	R_4	R_5	Yield %	M.P. (°C)	Appearance	Molecular weight	λ_{max} (nm)
2	H	H	$-CH_3$	H	H	50.3	190-194	Dull white ppt.	$C_{13}H_{13}N_3O_3S$	220, 266
3	$-CH_3$	H	$-CH_3$	H	$-CH_3$	52.7	207-210	Light yellow ppt.	$C_{15}H_{17}N_3O_3S$	220, 268
4	H	H	Br	H	H	49.1	217-224	Pinkish white ppt.	$C_{12}H_{10}BrN_3O_3S$	212, 263
5	H	H	$-NO_2$	H	H	42.1	193-197	Brown ppt.	$C_{12}H_{10}N_4O_5S$	214, 263
6	H	H	$-CH_3$	H	H	60.4	227-231	Dark yellow ppt	$C_{14}H_{13}N_3O_2$	212, 263
7	H	$-NO_2$	H	$-NO_2$	H	74.8	225-228	Dull white ppt	$C_{13}H_9N_5O_6$	215, 263

N -[(4-nitrobenzene)sulfonyl]pyridine-4-carbohydrazide 5

IR (cm-1): 3471.5 (NH str., amine), 3184.5 (NH str., amide), 1683.1 (CO str., nicotinyl), 1633.9 (C=C str., skeletal phenyl nucleus), 3041.3 (C-H str., aromatic), 1525.8, 1354.5 (NO_2 str., aromatic), Mass: m/z 323 $[M + H]^+$, ^1H NMR: (400 MHz, d_6-DMSO) δ ppm: 8.882-8.898 (d, 2H, CH of C_2 and C_6 of pyridine ring; $J = 6.4$), 7.797-7.830 (m, 3H, NH proton of N, CH of C_3 and C_5 of pyridine ring), 8.017-8.197 (m 4H, CH ofphenyl ring), 1.946-1.959 (d, 1H, NH proton of N□; $J = 5.2$),
CHN analysis: C 44.72, H 3.13, N 17.38, O 24.82, S 9.95

N -[(4-methylbenzoyl)]pyridine-4-carbohydrazide 6

IR (cm-1): 3370.0 (NH str., amine), 3093.6 (NH str., amide), 1695.2 (CO str., nicotinyl), 1637.3 (C=C str., skeletal phenyl nucleus), 3052.1 (C-H str., aromatic), 2969.4, 2637.1 (CH3 str., aromatic), Mass:m/z 256 $[M + H]^+$, ^1H NMR: (400 MHz, d_6-DMSO) δ ppm: 8.092-8.108 (d, 4H, CH of phenyl ring; J=6.4), 8.920-8.936 (m, 6H, NH proton of N and N□, CH of pyridine ring) 2.35 (s, 3H, CH_3), CHN analysis: C 65.87, H 5.13, N 16.46, O 12.54

N -[(3,5-dinitrobenzoyl)]pyridine-4-carbohydrazide 7

IR (cm-1): 3367.3 (NH str., amine), 3093.3 (NH str., amide), 1672.5 (CO str., nicotinyl), 1624.5 (C=C str., skeletal phenyl nucleus), 3053.0 (C-H str., aromatic), 1538.0, 1351.2 (NO_2 str., aromatic), Mass:m/z 332 $[M + H]^+$, ^1H NMR: (400 MHz, d_6-DMSO) δ ppm: 8.923-8.938 (d, 2H, CH of C_2 and C_6 of pyridine ring; $J = 6$), 7.983-8.078 (m, 4H, NH proton of N and N□, CH of C_3 and C_5 of pyridine ring), 9.021-9.120 (m, 3H, CH of phenyl ring), CHN analysis: C 47.14, H 2.74, N 21.14, O 28.98

DISCUSSION

Reaction mechanism

The underlying reaction mechanism can be predicted as follows:

The starting molecule 4-PCH has got three nitrogen, a tertiary N of pyridine ring (C_5H_4N), a secondary N of amide (CONH) and a primary N of amine moiety (NH_2) (fig. 1). Because of the two reasons that a) sp^3 hybridized N of aliphatic series is more reactive than sp^2 hybridized N of aromatic pyridine ring and b) the absence of removable proton in case of tertiary Nitrogen; the reaction will more likely to occur at the secondary and primary sites as compared to tertiary. As a general rule, primary N is more reactive than secondary so the reaction will certainly occur at this site (Wicks, 2007; McMurry, 2000).

As depicted form the Scheme 3, the reaction type is substitution reaction where the substrate served as Lewis base while reagent behaved as a Lewis acid. For a Lewis acid base reaction to occur, the attraction between the oppositely charged species is essential. To serve this purpose, acetone (with a dipole moment 3.0) was used. The partial negative end of the acetone attracts the hydrogen atom of the substrate molecule, resulting in the formation of negatively charged substrate and a proton (H^+) (fig. 2). The proton first snatches, then bonds to the chloride end of the reagent and forms HCl while the remaining part of reagent acquires a positive charge (fig.

Table 2: Pharmacological Screening of N□-Aryl-sulphonyl derivatives 2-5

S#	Behavioural parameter	Control	Test Compound 2	Test Compound 3	Test compound 4	Test Compound 5
a)	CNS Depression					
1	Motor activity	0	-	-	0	0
2	Ataxia/Staggering gate	0	0	0	0	0
3	Anesthesia	0	0	0	0	0
4	Respiratory rate	0	0	0	0	0
5	Paralysis	0	0	0	0	0
6	Screen griping	0	-	-	0	0
7	Sedation	0	0	0	0	0
b)	CNS stimulation					
1	Startle response	0	0	0	0	0
2	Motor activity	0	0	0	+	+
3	Coarse body tremors	0	0	0	0	0
4	Convulsions	0	0	0	0	0
5	Fasciculation	0	0	0	0	0
c)	CVS observations					
	Heart rate	0	0	0	0	0
d)	Eye observation					
1	Pupil size	0	0	0	0	0
2	Nystagmus	0	0	0	0	0
3	Lacrimation	0	0	0	0	0
4	Exophthalamus	0	0	0	0	0
5	Endophthalamus	0	0	0	0	0
e)	Ear Observation					
1	Blanching	0	0	0	0	0
2	Hyperemia	0	0	0	0	0
3	Cyanosis	0	0	0	0	0
f)	General Observation					
1	Groomig	0	0	0	0	0
2	Irritability	0	0	0	0	0
3	Tail erection	0	0	0	0	0
4	Spontaneous activity	0	-	0	0	+
5	Touch response	0	-	0	0	0
6	Sound response	0	0	0	0	0
7	Passivity	0	0	0	0	0
8	Circling motion	0	0	0	0	0
9	Writhing	0	0	0	0	0
10	Body tone	0	-	0	0	+
11	Climbing	0	0	0	+	0
12	Stereotype	0	0	0	0	0
13	Tail lashing	0	0	0	0	0
14	Vocalisation	0	0	0	0	0
15	Salivation	0	0	0	0	0
16	Diaarhoea	0	0	0	0	0

0 indicates normal
+ indicates increase with respect to normal, _ indicates decrease with respect to normal

Table 3: Pharmacological Screening of N□-benzoyl derivatives 6-7

S. No.	Behavioural parameter	Control	Test Compound 6	Test Compound 7
a)	CNS Depression			
1	Motor activity	0	0	-
2	Ataxia/Staggering gate	0	0	0
3	Anesthesia	0	0	0
4	Respiratory rate	0	0	0
5	Paralysis	0	0	0
6	Screen griping	0	0	0
7	Sedation	0	0	0
b)	CNS stimulation			
1	Startle response	0	0	0
2	Motor activity	0	+	
3	Coarse body ttremore	0	0	0
4	Convulsions	0	0	0
5	Fasciculations	0	0	0
c)	CVS observations			
	Heart rate	0	0	0
d)	Eye observation			
1	Pupil size	0	0	0
2	Nystagmus	0	0	0
3	Lacrimation	0	0	0
4	Exophthalamus	0	0	0
5	Endophthalamus	0	0	0
e)	Ear Observation			
1	Blanching	0	0	0
2	Hyperemia	0	0	0
3	Cyanosis	0	0	0
f)	General Observation			
1	Groomig	0	0	0
2	Irritability	0	0	0
3	Tail erection	0	0	0
4	Spontaneous activity	0	0	0
5	Touch response	0	0	0
6	Sound response	0	0	0
7	Passivity	0	0	0
8	Circling motion	0	0	0
9	Writhing	0	0	0
10	Body tone	0	0	+
11	Climbing	0	0	+
12	Stereotype	0	0	0
13	Tail lashing	0	+	0
14	Vocalisation	0	0	0
15	Salivation	0	0	0
16	Diaarhoea	0	0	0

0 indicates normal, + indicates increase with respect to normal, _ indicates decrease with respect to normal

3). The electron-efficient substrate bonds with electron-deficient reagent and forms a product (fig. 4) (Solomons and Fryhle, 2004; Finar, 1973; Sykes, 1986).

Compounds of benzoyl chloride series also followed the same reaction mechanism.

Chemistry

The IR spectra of all the arylsulphonyl derivatives (2-5)showed the presence of NH amine around 3440-3475cm^{-1} and NH amide around 3100-3185cm^{-1}.The spectra of benzoyl derivatives (6-7) revealed NH amine at 3367-3370cm^{-1}. The NH amide stretching was observed at3093cm^{-1}in all the compounds. CO nicotinyl was confirmed by astretching band around 1670-1700cm^{-1}.Peaks around 1624-1637cm^{-1} and 3030-3060 cm^{-1} indicated the stretching bands of C=C and CH of aromatic moiety. The bands in region of 2967-2971 cm^{-1} and 2637-2815cm^{-1}showed aromatic methyl group in compounds 2, 3and 6. The vibrational frequency of aromatic nitro group in compounds 5and 7produced2 bands; 1525-1538 cm^{-1} and 1354-135cm^{-1}, confirming its presence.

The molecular ion peaks of the synthesized compound were studied via FAB spectrum. Since the spectra were obtained in a positive mode therefore the respective ion peaks were at m/z292, 319, 356, 323, 256 and 332 for compounds 2-7 respectively.

NMR Spectra of arylsulphonyl derivatives revealed NH amine proton around δ 1.9-2.0ppm whereas in benzoyl derivatives this was shifted to δ 8.0-9.0 ppm because of the carbon-nitrogen bond. NH amide signal was present around δ 8.0-9.0 ppm in all the spectra. Proton of pyridine ring appeared at two different δ values, one at lower δ value 7.0-8.0 ppm correspond to protons of C_3 and C_5 while one at higher δ value 8.0-9.0 ppm correspond to C_2 and C_6 because of the presence of nitrogen atom. Protons of substituted phenyl ring appeared at δ 8.0-9.0 ppm. The singlet signal at δ 2.1, 2.2 and 2.3 ppm was indicative of a methyl group in compound 2, 3and 6 respectively.

Pharmacological screening

When compared with the control group at the dose of 25mg/Kg, no characteristic response was noticed except for CNS activity. It was observed that the test compounds 2, 3 and 7 produced CNS depression whereas test compounds 4, 5 and 6stimulated the CNS via motor activity.

From the obtained results, structure activity relationship can be accomplished as:

1. The arylsulphonyl derivatives of PCH (2 and 3) showing decreased motor activity contained *p*-CH_3 and *o,p*-CH_3 groups respectively while compounds 4 and 5having *p*-Br and *p*-NO_2 groups increased the motor activity.
2. In case of benzoyl derivatives, interesting pattern was observed where *p*-CH_3 substitution in compound 6was found augmenting the motor activity and *m*-NO_2 groups in compound 7 reduced the motor activity.

It can be suggested that the effects produced were not only due to the nature of the functional groups but also the positions at which they are attached.

CONCLUSION

Six new derivatives of 4-pyridine carboxylic acid hydrazide were synthesized successfully. Upon pharmacological screening, all the synthesized derivatives showed activity on CNS, which was observed by the change in locomotion of mice. However more experiments are needed to explore the mechanism of action of these compounds.

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