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Synthesis and *In-vivo* Analgesic Activity of 1,2,4-Thiadiazole Derivatives

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Abstract: A new series of Mannich bases MK8-12 has been synthesized from 1, 2, 4- thiadiazole by Mannich reaction. All the synthesized compounds of the series displayed, remarkable analgesic activity in comparison to standard drug diclofenac sodium. In the synthesized thiadiazole derivatives MK-8 & MK-10 showed activity at 20mg/kg . MK-9 & MK-11 are considered as most active compounds as they protected 60.85% & 59.55% respectively of animals at a dose of 20mg/kg. Chemical structures of all the new compounds were established by IR, NMR, MS spectroscopy and elemental analysis. Most of these new compounds showed appreciable activity against the test, and emerged as potential molecules for further development.
Key words: Thiadiazole , diclofenac sodium, spectroscopy, analgesic activity.

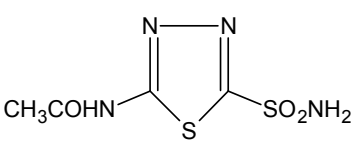
INTRODUCTION:

Thaidiazoles represent an important class of medicinally active compounds that exhibits wide variety of biological activities. Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphur atom. They occur in nature in four – isomeric forms viz. 1,2,3- thiadiazole, 1,2,5-thiadiazole , 1,2,4- thiadiazole, 1,3,4- thiadiazole.

Mannich bases are used as prodrugs. A series of 1, 2, 4- thiadiazoles have shown anti- inflammatory activity[1, 2, 3] and 1, 2, 4 thiadiazoles have shown anti convulsant activity[4,5].In view of biological potential of 1,2,4-thiadiazoles and their Mannich bases therefore mannich bases[6] of 1, 2, 4-thiadiazole were prepared.

N-[5-(aminosulfonyl)-1, 3, 4 – Thiadiazole-2-yl]-acetamide **[1]** is a diuretic mainly used for reduction of intraocular tension in glaucoma and frequently used in petitmal epilepsy[7].

Structure of N-[5-(aminosulfonyl)-1,3,4 – Thiadiazole-2-yl]-acetamide **[1].**



[1]

1, 2, 4 thiadiazoles are highly potent inhibitors of human immunodeficiency virus type 1 HIV-1) replication[8].

The synthesis of 1,2,4- thiadiazole has attracted a great deal of interest through the years due to their biological activities such as antimicrobials[9-14], anti-cancer[15-17], anti-oxidant, anti-depressant[18-19], radio protective, analgesic and anti-leishmanial. 1, 2, 4- thiadiazole are widely found in bioorganic and medicinal chemistry with application in drug discovery and development for treatment of human leukemia cell[20], such as cathepsin B inhibitors[21], allosteric modulators[22], factor XIIIa inhibitors[23], non ATP competitive glycogen synthase kinase 3β inhibitors. Some of these show intense muscarinic and cardio protective activities. Therefore new 1, 2, 4-thiadiazoles have been synthesized .

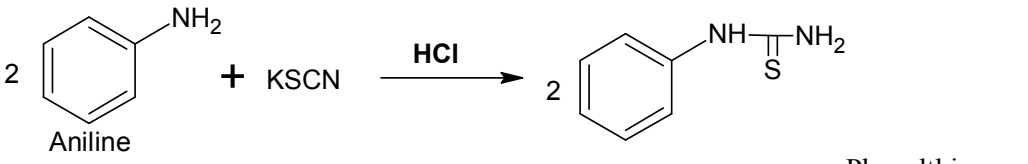
We have synthesized many derivatives of 1, 2, 4-thiadiazole by using Mannich reaction.

The compounds have been synthesized by following scheme.

SCHEME1.

(I)

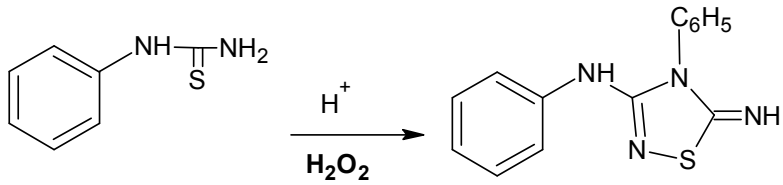
a)



Aniline

Phenylthiourea

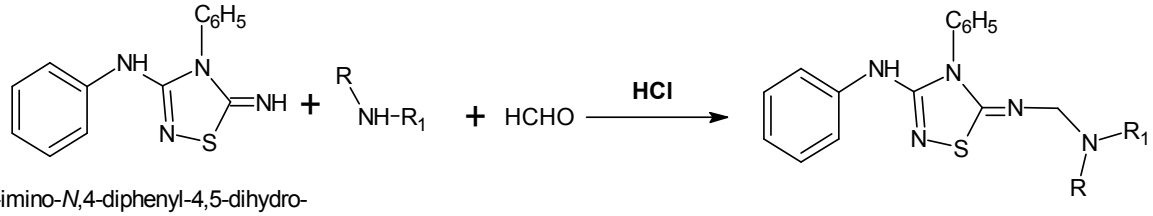
b)



Phenylthiourea

5-imino-*N*,4-diphenyl-4,5-dihydro-1,2,4-thiadiazol-3-amine

c)



5-imino-*N*,4-diphenyl-4,5-dihydro-1,2,4-thiadiazol-3-amine

Mannich base Derivative

EXPERIMENTAL SECTION

MATERIAL AND METHODS:

All the chemicals used during the practical work were obtained from the Mark India (pvt.) ltd., S.D.Fine limited, Loba chemicals, Ranbaxy fine chem. & CDH. The chemicals and solvent used are of synthetic and AR grade respectively.

Melting points were determined in Thiele's melting point tube using liquid paraffin by open capillary method and are uncorrected. TLC of the compound was taken by using silica G as a spreading agent & the solvent system used was (Benzene: Ethyl acetate) (4:1). The IR spectra were recorded using the KBr pellets. The ^{1}H NMR spectra were taken and chemical shifts δ values are expressed in ppm related to tetra methyl silane (TMS) as an internal standard & Elemental analysis were carried out to identified and characterized the synthesized compounds .

PROCEDURES:

I)SYNTHESIS OF MANNICH BASE DERIVATIVES:

a)FORMATION OF PHENYLTHIOUREA FROM ANILINE:

To aniline (12.5mL), concentrate hydrochloric acid (12.5mL) was added and the solution was warmed. A saturated solution of potassium thiocyanate in water (15gm in 30mL) was added slowly in above solution. The mixture was boiled until the solution got turbid. The turbid solution was poured in cold water. The separated precipitate as phenyl thiourea was filtered. Rf =0.88, m.p. = 153-155 (^{0}**C)** , Yield: 12gm,

b) PREPARATION OF 5-IMINO-N, 4-DIPHENYL-4, 5-DIHYDRO-1, 2, 4-THIADIAZOL-3-AMINE:

Phenylthiourea (5gm, 0.328mole) was taken, dissolved in water and HCl (2mL) was slowly added. After that

H_2O_2 in excess (11mL) was slowly added in the solution with continuous stirring. Solution was kept a side at room temperature (rt) approximately for 2 hr. Then the solution was filtered and sulphate (yellow color) was discarded and filtrate was taken. Filtrate was basifying with ammonia and the solid product was filtered.
Yield = 3.5gm, m.p. = 138-140(^{0}C), Rf = 0.23,IR υ (cm^{-1}):N-H(s) 3444 cm^{-1},C=C(s) in Ar 1633 cm^{-1} ,C-N(d) in Ar 914 cm^{-1} ,C-H in Ar 753 cm^{-1} ,Ar-H(s) 3219 cm^{-1} ,N-H(s) in sec.amine 3362 cm^{-1} , C-S 600 cm^{-1} ,C-N 1311 cm^{-1} C=N in ring 1420 cm^{-1} , ^{1}H-NMR δ (ppm) 6.46-7.26(s, Ar-CH), 4.0(s, C-NH) , ^{13}C-NMR δ (ppm): 115-128(Ar-CH),162.8(Ar-CH-N) Calculated (%) for $C_{14}H_{12}N_4S$, C (62.66) H(4.51) N(20.88) S(11.95) Found(%) C(62.04) H (4.10) N (20.40) S (11.45).

C) REACTION OF 5-IMINO-N, 4-DIPHENYL-4, 5-DIHYDRO-1, 2, 4-THIADIAZOL-3-AMINE WITH DIFFERENT SECONDARY AMINES:
1, 2,4-Thiadiazole(1gm,0.0037moles) was dissolved in methanol and equimolar quantity of different secondary amines ($RNH\text{-}R_1$) was taken in 250 mL of round bottom flask, formaldehyde(5mL) and HCl (2mL) was added in the solution. Then the whole reaction mixture was refluxed for 3 hr. The reaction mixture was filtered and the filtrate was cooled in chilled water with continuous stirring for 10 minutes. Then solid product was filtered and dried after washing with water.

MANNICH BASES
MK8-12.
N,N-diethyl-N'-[4-phenyl-3-(phenylamino)-1,2,4-thiadiazol-5(4H)-ylidene]methanediamine:(MK-8)
%Yield = 68.18,m.p.=110-112 ºC, Rf = 0.15 IR υ (cm^{-1}):N-H(s) 3456 cm^{-1},C-N(d) in Ar 910 cm^{-1} ,Ar-H(s) 3210 cm^{-1} ,N-H(s) in sec.amine 3351 cm^{-1} , C-S 614 cm^{-1} ,C-N 1321 cm^{-1} C=N in ring 1423 cm^{-1} , ^{1}H-NMR δ (ppm) 6.46-7.26(s,Ar-CH),4.00(m,Ar-C-NH),2.4(s,N-CH2-N), ^{13}C-NMRδ(ppm): 146.7(Ar-C),115.1-128.5(Ar-CH),162.8-163(C=N),Calculated (%) for $C_{19}H_{25}N_5S$ C(64.56) H(6.56) N(19.81) S(9.07)
Found (%) C (64.14) H (6.12) N (19.41) S (9.40)

N, 4-diphenyl-5-[(piperazin-1-ylmethyl) imino]-4, 5-dihydro-1, 2, 4-thiadiazol-3-amine :(MK-9)
%Yield : 63.50, m p :125-127ºC, Rf : 0.29 ,IR υ (cm-1):N-H(s) 3449 cm-1, C=N in ring 1420 cm-1,C-N(d) in Ar 919 cm-1 ,Ar-H(s) 3212 cm-1 ,N-H(s) in sec.amine 3342 cm-1 , C-S 612 cm-1 ,C-N 1331 cm-1,N-H in piperazine ring 3227 cm-1. ^{1}H-NMR δ (ppm): 6.46-7.26(s,Ar-CH),4.00(m,Ar-C-NH),2.4 (s,CH2),2.0(s,NH amine),2.48(m,N-CH_2) ^{13}C-NMRδ(ppm): 146.7(Ar-C),115.1-128.5(Ar-CH), 162.8-163(C=N), 64.1(aliphatic N-C-N), Calculated (%) for$C_{19}H_{24}N_6S$, C (62.27) H(6.05) N(22.93) S(8.75) Found (%) C (62.17) H (6.50) N (22.44) S (8.70)

N,4-diphenyl-5-[(piperidin-1-ylmethyl)imino]-4,5-dihydro-1,2,4-thiadiazol-3-amine: (MK-10)
%Yield =65, m. p.: 120-122ºC, Rf : 0.20, IR υ (cm-1):N-H(s) 3421 cm-1, C=N in ring 1419 cm-1,C-N(d) in Ar 917 cm-1 ,Ar-H(s) 3212 cm-1 ,N-H(s) in sec.amine 3356 cm-1 , C-S 615 cm-1 ,C-N 1330 cm-1. 1H-NMR δ (ppm): 6.46-7.01(s,Ar-CH),4.00(m,Ar-C-NH),2.4(s,CH2), 2.24(m,N-CH_2) 13C-NMRδ(ppm): 146.7(Ar-C),115.3-128.5(Ar-CH), 162.5-163(C=N), 64.4(aliphatic N-C-N), Calculated (%) for C20H25N5SC(65.72) H(6.34) N(19.16) S(8.77), Found (%)C (65.42) H(6.43) N (19.16) S (8.47)

5-[(morpholin-4-ylmethyl)imino]-N,4-diphenyl-4,5-dihydro-1,2,4-thiadiazol-3-amine: (MK-11)
%Yield =54.34,m. p .=116-118ºC, Rf =0.44, IR υ (cm-1):C-S 605 cm-1 ,C-N 1328 cm-1,N-H(s) 3420 cm-1, C=N in ring 1419 cm-1,C-N(d) in Ar 909 cm-1 ,Ar-H(s) 3210 cm-1 ,N-H(s) in sec.amine 3350 cm-1,C-O-C 1153 cm-1. ^{1}H-NMR δ (ppm): 6.43-7.25(s,Ar-CH),4.01(m,Ar-C-NH),2.38(s,CH2),2.1(m,N-CH_2),3.61(s,H_2C-O-CH_2) ^{13}C-NMRδ(ppm): 146.6(Ar-C),115.0-128.5(Ar-CH), 162.4-163(C=N), 64.4(aliphatic N-C-N),71.5(C-O-C)Calculated (%) for C19H23N5O S,C(62.10) H(5.76%) N(19.06) O(4.35) S(8.73),Found C(62.14%) H(5.70) N(19.16) O(4.30) S(8.69).

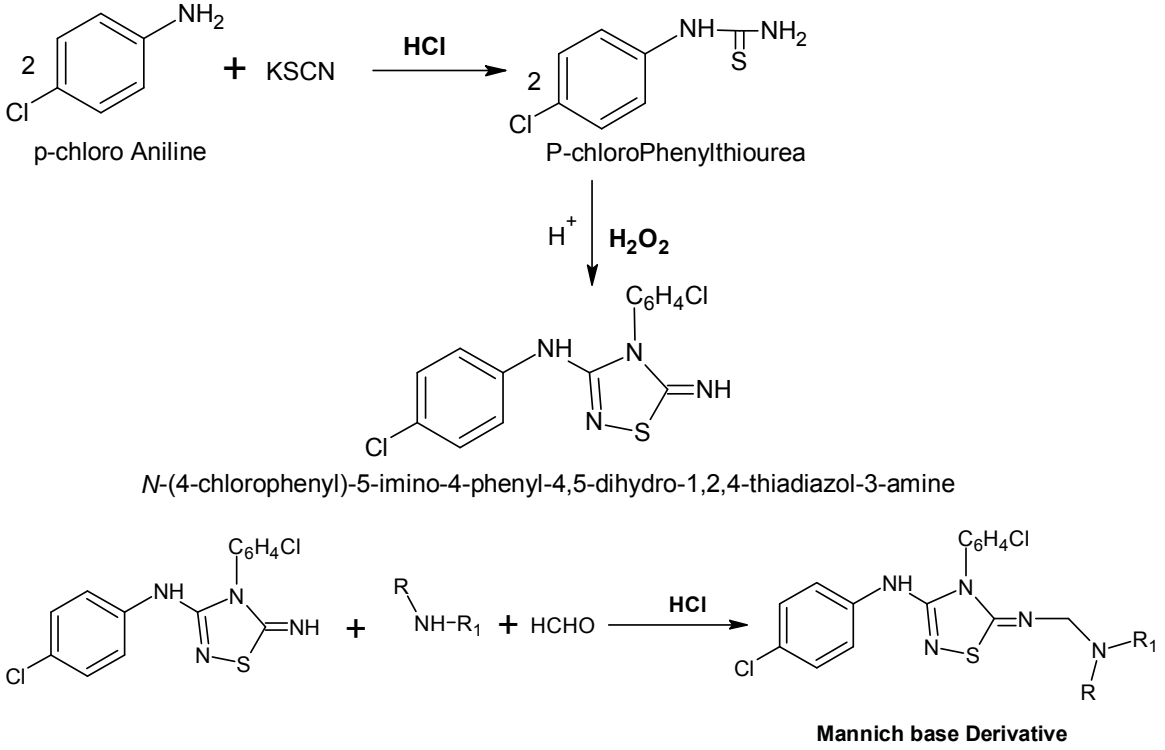
***N,N*-dimethyl-*N*'-[4-phenyl-3-(phenylamino)-1,2,4-thiadiazol-5(4*H*)- ylidene]methanediamine: (MK-12)**
%Yield : 54.91,m. p. : 130-132ºC, Rf : 0.38,IR υ (cm-1):C-S 605 cm^{-1} ,C-N 1312 cm^{-1},N-H(s) 3420 cm^{-1}, C=N in ring 1429 cm^{-1},C-N(d) in Ar 918 cm^{-1} ,Ar-H(s) 3210 cm^{-1} ,N-H(s) in sec.amine 3427 cm^{-1}. ^{1}H-NMR δ (ppm): 6.42-7.01(s,Ar-CH),4.00(m,Ar-C-NH),2.4(s,CH2), 2.31(m,N-CH_2) ,3.31(s,H_2C-O-CH_2) 13C-NMRδ(ppm): 146.6(Ar-C),115.02-128.8(Ar-CH), 162.6-163(C=N), 64.4(aliphatic N-C-N),71.5(C-O-C) Calculated (%) for $C_{17}H_{21}N_5S$ C(62.74) H(5.88) N(21.52) S(9.85),Found C(62.71) H(5.80) N(21.56) S(9.81).

TABLE 1: PHYSICAL PROPERTIES OF THIADIAZOLE DERIVATIVES:

S.N.	Code	Mol.Formula	Mol.Wt.	m.p.(ºC)	Rf.Value	%Yield
1.	MK-8	$C_{19}H_{25}N_5S$	355.50	110-112	0.15	68.18
2.	MK-9	$C_{19}H_{24}N_6S$	368.49	125-127	0.29	63.50
3.	MK-10	$C_{20}H_{25}N_5S$	367.51	120-122	0.20	65.00
4.	MK-11	$C_{19}H_{23}N_5OS$	369.48	116-118	0.44	54.34
5.	MK-12	$C_{17}H_{21}N_5S$	327.44	130-132	0.38	54.91

REACTION OF CHLORO DERIVATIVE OF 1, 2, 4- THIADIAZOLE WITH DIFFERENT SECONDARY AMINES BY USING MANNICH REACTION.

SYNTHETIC SCHEME:



General procedure for the preparation of p-chlorophenylthiourea from p-chloroaniline:

To p-chloroaniline (17.85gm), concentrate hydrochloric acid (12.5mL) was added and the solution was warmed. A saturated solution of potassium thiocyanate in water (15gm in 30mL) was added slowly in above solution. The mixture was boiled until the solution got turbid. The turbid solution was poured in cold water. The separated precipitate as p-chlorophenylthiourea was filtered.

Yield : 77%, Melting Point: 165-167, Rf:0.86

Reaction of p-chlorophenylthiourea with H_2O_2:

p-Chlorophenylthiourea 5gm, 0.0268 moles) was taken, dissolved in water and HCl (2mL) was slowly added. After that H_2O_2 in excess (11mL) was slowly added in the solution with continuous stirring. Solution was kept a side at room temperature approximately for 2 hr. After that the solution was filtered and solid residue was taken and the filtrate was discarded. The solid residue was then washing with carbon disulphide (CS_2) and filtrate was discarded, solid product was dried.

Yield: 2.5gm ,Melting Point : 190-192 ^{0}C , Rf : 0.61 , IR υ (cm-1):C-Cl(s) 756 cm^{-1} ,C-S 605 cm^{-1} ,C-N 1314 cm^{-1},N-H(s) 3421 cm^{-1}, C=N in ring 1427 cm^{-1},C-N(d) in Ar 913 cm^{-1} ,Ar-H(s) 3210 cm^{-1} ,N-H(s) in sec.amine 3310 cm^{-1} ^{1}H-NMR δ (ppm): 13C-NMRδ(ppm): Calculated % for C(55.53) H(3.66) Cl(11.71) N(18.50) S(10.59),Found (%) C(55.57) H(3.60) Cl(11.75) N(18.46) S(10.55)

Reaction of N-(4-chlorophenyl)-5-imino-4-phenyl-4,5-dihydro-1,2,4-thiadiazol-3-amine with different secondary amines by using Mannich Reaction:

N-(4-chlorophenyl)-5-imino-4-phenyl-4,5-dihydro-1,2,4-thiadiazol-3-amine(1gm,0.0033moles) was dissolved in methanol and equimolar quantity of different secondary amines (NHRR1) was taken in 250 mL of round bottom flask, formaldehyde(5mL) and HCl(2mL) was added in the solution. After that the whole reaction mixture was refluxed for 3 hr.The reaction mixtures were filtered and the filtrate was cooled in chilled water with continuous stirring for 10 minutes. Then the solid product was filtered and dried after washing with water.

N-(4-chlorophenyl)-4-phenyl-5-[(piperazin-1-ylmethyl)imino]-4,5-dihydro-1,2,4-thiadiazol-3-amine :(MK-20)

%Yield: 42.42,Melting Point : 220-222ºC,Rf : 0.59,IR (KBr,cm^{-1}):C-Cl(s) 773cm^{-1} ,C-S 615 cm^{-1} ,C-N 1324 cm^{-1},N-H(s) in piperazine 3213 cm^{-1}, C=N in ring 1430 cm^{-1},C-N(d) in Ar 913 cm^{-1} ,Ar-H(s) 3210 cm^{-1} , ^{1}H-NMR δ (ppm): 13C-NMRδ(ppm): Calculated % for $C_{19}H_{21}ClN_6S$ C(56.92%) H(5.28%) Cl(8.84%) N(20.96%) S(8.00%)
Found (%) C(56.96%) H(5.24%) Cl(8.80%) N(20.92%) S(8.40%)

N-(4-chlorophenyl)-5-[(morpholin-4-ylmethyl) imino]-4-phenyl-4, 5-dihydro-1, 2, 4-thiadiazol-3-amine :(MK-21)

%Yield : 44.69, m. p . : 200-202ºC ,Rf : 0.67,IR (KBr,cm^{-1}):C-Cl(s) 757cm^{-1} ,C-S 621 cm^{-1} ,C-N 1324 cm^{-1},N-H(s) in piperazine 3213 cm^{-1}, C=N in ring 1430 cm^{-1},C-N(d) in Ar 908 cm^{-1} ,Ar-H(s) 3210 cm^{-1} ,N-H(s) in sec.amine 3310 cm^{-1} ,C-O-C 1148 cm^{-1}. ^{1}H-NMR δ (ppm): 13C-NMRδ(ppm): Calculated % fo r$C_{19}H_{20}ClN_5OS$,C(56.78%) H(5.02%) Cl(8.82%) N(17.43%) O(3.98%) S(7.98%),Found C(56.74%) H(5.42%) Cl(8.86%) N(17.47%) O(3.94%) S(7.94%)

N-(4-chlorophenyl)-4-phenyl-5-[(piperidin-1-ylmethyl)imino]-4,5-dihydro-1,2,4-thiadiazol-3-amine:(MK-22)

%Yield : 39.39, m. p.: 210-212ºC, Rf : 0.64,IR (KBr,cm^{-1}):C-Cl(s) 781cm^{-1} ,C-S 627 cm^{-1} ,C-N 1316 cm^{-1} , C=N in ring 1432 cm^{-1},C-N(d) in Ar 908 cm^{-1} ,Ar-H(s) 3210 cm^{-1} ,N-H(s) in sec.amine 3310 cm^{-1} . ^{1}H-NMR δ (ppm): 13C-NMRδ(ppm): Calculated % for $C_{20}H_{22}ClN_5S$ C(60.06%) H(5.54%) Cl(8.86%) N(17.51%) S(8.02%),Found C(60.42%) H(5.58%) Cl(8.90%) N(17.55%) S(8.40%)

N'-{3-[(4-chlorophenyl)amino]-4-phenyl-1,2,4-thiadiazol-5(4H)-ylidene}-N,N-diethyl methanediamine:(MK-23)

%Yield : 34.84, m. p.: 225-227ºC, Rf : 0.60 ,IR (KBr,cm^{-1}):C-Cl(s) 791cm^{-1} ,C-S 627 cm^{-1} ,C-N 1316 cm^{-1} ,C-N(d) in Ar 908 cm^{-1} ,Ar-H(s) 3210 cm^{-1} ,N-H(s) in sec.amine 3330 cm^{-1} . N-H(s) 3427 cm^{-1}, C=N in ring 1419 cm^{-1}. ^{1}H-NMR δ (ppm): 13C-NMRδ(ppm): Calculated % for $C_{19}H_{22}N_5S$,C(58.83%) H(5.72%) Cl(9.14%) N(18.05%) S(8.27%),Found C(58.87%) H(5.68%) Cl(9.18%) N(18.40%) S(8.23%)

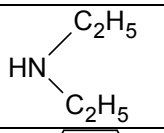
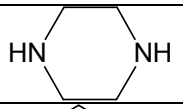
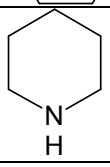
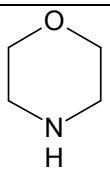
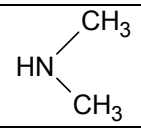
N'-{3-[(4-chlorophenyl)amino]-4-phenyl-1,2,4-thiadiazol-5(4H)-ylidene}-N,N-dimethyl methanediamine:(MK-24)

%Yield : 45,m. p : 195-197ºC, Rf : 0.69 ,IR (KBr,cm^{-1}):C-Cl(s) 761cm^{-1} ,C-S(s) 607 cm^{-1} ,C-N 1306 cm^{-1} ,C-N(d) in Ar 918 cm^{-1} ,Ar-H(s) 3218 cm^{-1} ,N-H(s) in sec.amine 3316 cm^{-1} . N-H in N-CH_3 2931 cm^{-1}, C=N in ring 1422 cm^{-1}. ^{1}H-NMR δ (ppm): 13C-NMRδ(ppm): Calculated % for $C_{17}H_{18}ClN_5S$,C(56.74%) H(5.04%) Cl(9.85%) N(19.46%) S(8.91%),Found C(56.70%) H(5.40%) Cl(9.81%) N(19.50%) S(8.95%).

TABLE 2:PHYSICAL PROPERTIES OF P-CHLORO DERIVATIVES OF 1,2,4- THIADIAZOLE.

S.N.	Code	Molecular Formula	Molecular Weight	Melting point(ºC)	Rf. Value	%Yield
1.	MK-20	$C_{19}H_{21}ClN_6S$	400.92	220-222	0.59	42.42
2.	MK-21	$C_{19}H_{20}ClN_5OS$	401.91	200-202	0.67	44.69
3.	MK-22	$C_{20}H_{22}ClN_5S$	399.94	210-212	0.64	39.39
4.	MK-23	$C_{19}H_{22}N_5S$	387.92	225-227	0.60	34.84
5.	MK-24	$C_{17}H_{18}ClN_5S$	359.88	195-197	0.69	45.00

TABLE 3:

	Secondary Amines	Structure
1.	**Diethyl amine**	
2.	**Piperazine**	
3.	**Piperidine**	
4.	**Morpholine**	
5.	**Dimethylamine**	

BIOLOGICAL ACTIVITY:

METHOD FOR ASSESSMENT OF ANALGESIC ACTIVITY:

The thiadiazole derivatives were evaluated for analgesic activity against acetic acid induced writhing **.**Diclofenac sodium was used as the standards drug. Acetic acid induced writhing in mice method (modified Koster's test) **[71 & 72]** was used to determine analgesic activity in vivo. Analgesic activity was determined by calculating total no of writhing, following intraperitonial (I.P) administration of 0.6% (0.1ml/10g) acetic acid in mice. Albino mice of either sex (25-30g) were used.

Synthesized compounds ((MK-8, MK-9, MK-10, MK-11, and MK-12) were administered intraperitonialy (0.5ml) as a suspension in sterile 0.9% DMSO solution as vehicle. Diclofenac sodium (20mg/kg) was used as the standard drug under same conditions. Acetic acid solution was administered intraperitonialy 30 min after administered of the compounds. 10 min after intraperitonial injection of the acetic acid solution, the number of writhing per animal was recorded for 20 min. Control animals received an equal volume of vehicle.

Results of Percentage Analgesic activity of compounds was calculated using following formula & the results were shown in table.

Statistical analysis

Values for activities were expressed as mean after drug administration ± SEM. The significance of difference between means was determined by Dennett's t-test and values of $P<0.05$ were considered significant and $P<0.01$ as highly significant.

The results are summarized in table.

$$\% \text{ Analgesic Activity} = \left[\frac{\text{No. of writhings for control} - \text{No. of writhings for test compound}}{\text{No. of writhings for control}} \right] \times 100$$

TABLE 4:

Sr.No	Derivatives	Dosage	Number of writhings in 20 minutes (mean ± SEM)	%Analgesic* activity
1	Control	Vehicle	73.33 ± 2.82	0
2	MK-8	20 mg/kg	33.66± 2.82	54.09**
3	MK-9	20 mg/kg	32.33 ± 2.31	60.85**
4	MK-10	20 mg/kg	31.33 ± 3.41	56.22**
5	MK-11	20 mg/kg	29.66 ± 1.41	59.55**
6	MK-12	20 mg/kg	51.66 ± 3.50	29.55**
7	Diclofenac sodium	20 mg/kg	9.66 ± 0.53	86.82***

N=6; student t-test; *P≤0.05; **P≤0.01; ***P≤0.001 when compared with control

RESULTS AND DISCUSSION

The synthesized compounds were screened for analgesic activity. In the synthesized thiadiazole derivatives MK-8 & MK-10 showed activity at 20mg/kg. MK-9 & MK-11are considered as most active compounds as it protected 60.85% & 59.55% respectively of animals at a dose of 20mg/kg.However MK-12 is the least active compound and thus possesses less analgesic properties.

In conclusion MK-12 emerges as a lead compound from these studies and further molecular modification of this compound could lead to better drugs.

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