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SYNTHESIS, CHARACTERIZATION, PHARMACOLOGICAL AND ANTIMICROBIAL STUDIES OF SCHIFF AND MANNICH BASES.

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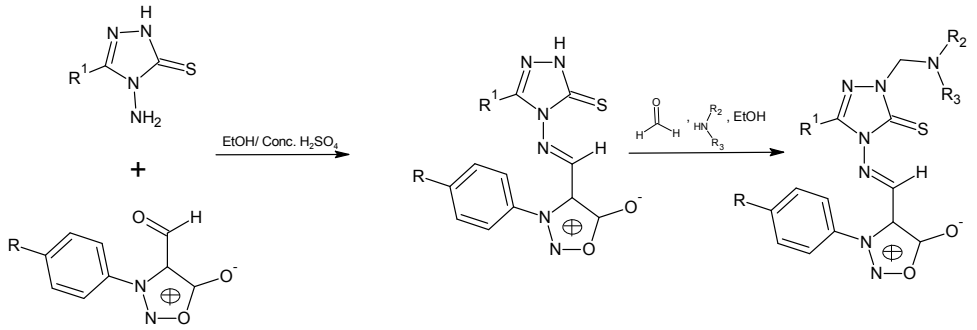
ABSTRACT
A novel series of 3-arylsydnone bearing Mannich bases **4** was prepared from the Schiff bases **3** by amino methylation with primary/secondary amine and formaldehyde. All the newly synthesized compounds were screened for their antibacterial, antifungal, analgesic, anti-inflammatory and CNS depressant activity studies. Few of the Schiff and Mannich bases showed significant CNS depressant, anti-inflammatory, analgesic and antibacterial activity compared with the standard employed.

KEYWORDS: Sydnone derivatives; Mannich bases; Schiff bases; Anti-inflammatory; Analgesic; CNS depressant activity.

1. INTRODUCTION
Mesoionic compounds are of special interest among heterocycles due to their unusual electronic structure. Sydnones are the most important representatives of mesoionic compounds because they possess physiological activity of different types depending on substituent in the heterocyclic ring [I,II]. Many sydnone compounds are known to have varied biological and pharmacological activities particularly sydnone-4-heterocycles[III,IV]. They exhibit central nervous system activity, convulsant and anticonvulsant activities, antimicrobial, antimalarial, analgesic, antitumour, antifungal and anti-inflammatory activities[V-VII]. The 1,2,4-triazole nucleus has been incorporated into a wide variety of therapeutically interesting drug candidates including H_1/H_2 histamine receptor blockers, cholinesterase active agents, CNS stimulants, anti-anxiety agents and sedatives[VIII-IX].
After the early discovery by Mannich, Mannich bases have become important tools for the synthesis of variety of heterocyclic compounds. Mannich bases can either directly be employed or used as intermediates in chemical synthesis. They find a significant role in the field of Pharmaceutical industry. The versatile Pharmacological activities exhibited by these compounds have been described many times in the literature. Studies on antineoplastic drugs,

analgesic drugs, antibiotic drugs, antiinflammatory etc, including labelled molecules have received particular attention in the recent past.

Prompted by these observations and in continuation of our search for biologically active sydnone-4-heterocycle[X-XI], we focused our attention on the synthesis of some Schiff bases and their Mannich derivatives containing both triazole and sydnone moieties with a view to evaluate their pharmacological activities.



2. EXPERIMENTAL

Material

Melting points were determined by open capillary method and are uncorrected. All compounds were analyzed for C, H, and N. IR spectra (KBr disc) were recorded on a JASCO FT IR 430 spectrophotometer. ^{1}H-NMR Spectra were recorded on Bruker AC 300F (300MHz) NMR spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and tetramethyl silane as internal standard. The chemical shifts are expressed in δ scale downfield from TMS and proton signals are indicated as s = singlet, d = doublet, t = triplet, m = multiplet. Mass spectra were recorded on a Jeol JMS-D 300 mass spectrometer operating at 70eV. TLC was carried out on silica gel plates using benzene-methanol as eluent.

3-Arylsydnones were prepared following the literature method[XII]. Formylation was carried out with N-methylformanilide and phosphorous oxychloride according to the method of Thoman et al[XIII]. 3-Aryl/aryloxymethyl-4-amino-5-mercapto-1,2,4-triazole **1** were prepared as per the procedure reported in literature[XIV,XV].

General procedure for preparation of 3-substitited -4-(3-aryl-4-sydnolidene) amino-5-mercapto-1, 2, 4- triazoles (Schiff bases) (3)

To a solution of 3-substituted -4- amino-5-mercapto-1, 2, 4- triazoles (**3)** (0.01 mol) in absolute ethanol (25 ml), was added 3-aryl-4-formylsydnone **(2)** (0.01 mol). Concentrated sulphuric acid (0.5 ml) was added to this reaction mixture. The contents were stirred at room temperature for 1-2 hours. The solid product separated was dried and recrystallized from suitable solvent. The yield, melting point and other characterization date of the compound prepared as above are given in **Table I.**

3-Phenyl-4-(3-phenyl-4-sydnolidene) amino 5-mercapto-1,2,4-triazole **(3a)**

IR (KBr cm-1) 3092 (Ar-H), 1763 (sydnone C=O), 1591 (-N=CH); ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 6.9-7.1 (m, 5H, Ar-H), 7.28-7.32 (m, 5H, Ar-H), 10.12 (s, 1H, -N=CH), 13.98 (s, 1H, SH). MS : m/z: 364.20 [M^++1].

3-Phenyl-4-(3-p-tolyl-4-sydnolidene) amino 5-mercapto-1,2,4-triazole **(3b)**
IR (KBr cm-1) 3085 (Ar-H), 1771 (sydnone C=O), 1593 (-N=CH); ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 2.48 (s, 3H, CH_3), 7.26 (d, 2H, J=7.71 Hz, meta protons of p-tolyl), 7.38 (d, 2H, J=7.78 Hz, ortho protons of p-tolyl), 7.52-7.56(m, 5H), 10.16 (s, 1H, N=CH), 13.92 (s, 1H, SH). MS : m/z: 378.34 [M^++1].

3-p-Chlorophenoxymethyl-4-(3-phenyl-4-sydnolidene) amino 5-mercapto-1,2,4-triazole **(3c)**
IR (KBr cm-1) 2976 (Ar-H), 1761(sydnone C=O), 1589 (-N=CH); ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 4.2 (s, 2H, O-CH_2-), 7.22-7.28 (m, 5H, Ar-H), 7.36 (d, 2H, J=8.1 Hz, meta protons of p-chlorophenyl), 7.42 (d, 2H, J=8.12 Hz, ortho protons of p-chlorophenyl), 10.08 (s, 1H, -N=CH), 13.86 (s, 1H, SH). MS : m/z: 428.9/431 [M^++1]/ [M^++3]..

3-p-Chlorophenoxymethyl-4-(3-p-tolyl-4-sydnolidene) amino 5-mercapto-1,2,4-triazole **(3d)**
IR (KBr cm-1) 2979 (Ar-H), 1765(sydnone C=O), 1589 (-N=CH); ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 2.49 (s, 3H, CH_3), δ, 4.09 (s, 2H, O-CH_2-), 6.94 (d, 2H, J=7.2 Hz meta protons of p-tolyl), 7.24 (d, 2H, J=7.24 Hz, ortho protons of p-tolyl), 7.34 (d, 2H, J=8.24 Hz, meta protons of p-chlorophenyl), 7.41 (d, 2H, J=8.28 Hz, ortho protons of p-chlorophenyl), 10.4 (s, 1H, N=CH), 14.01 (s, 1H, SH). MS : m/z: 443.3/445.2 [M^++1]/ [M^++3].

General procedure for preparation of 1-aminomethyl-3-substitited -4-(3-aryl-4-sydnolidene) amino-5-mercapto-1, 2, 4- triazoles-5-thiones (Mannich bases) (4)
A mixture of Schiff bases **(3)** (0.01mol) and formaldehyde 40% (1.5 ml) in ethanol (20 ml) was taken and to this solution suitable primary or secondary amine (0.01 mol) in ethanol (10 ml) was added and stirred at room temperature. The solid product gets separated within half an hour. The stirring was continued for another four hours. Finally, the product was collected by filtration, washed with ethanol and dried. It was further purified by recrystallization from suitable solvent. The characterization data of these newly synthesized Mannich bases are given in **Table-II.**

1-p-Chloroanilinomethyl-3-phenyl -4-(3-phenyl-4-sydnolidene) amino-5-mercapto-1, 2, 4-triazoles-5-thiones **(4a)**
IR (KBr) γ/cm^{-1}: 1294 (C=S), 1500 (C=C), 1587 (C=N), 1720 (C=O), 2920 (C-H), 2920 (Ar-H), 3180 (N-H). ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 5.16 (s, 2H, -N-CH_2-N-), 5.8 (s, 1H, -NH), 6.88 (d, 2H, J=8.2 Hz, meta protons of p-chlorophenyl), 7.1(d, 2H, J=8.18 Hz, ortho protons of p-chlorophenyl), 7.2-7.28 (m, 5H, Ar-H), 7.38-7.46 (m, 5H, Ar-H), 10.1 (s, 1H, N=CH). m/z: 504.2/506.3 [M^++1] [M^++3]

1-Morpholinomethyl-3-phenyl -4-(3-phenyl-4-sydnolidene) amino-5-mercapto-1, 2, 4-triazoles-5-thiones **(4b)**
IR (KBr) γ/cm^{-1}: 1312 (C=S), 1492 (C=C), 1588 (C=N), 1712 (C=O), 2920 (C-H), 2920 (Ar-H).^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 2.68 (t, 4H ,morpholine N(CH_2)$_2$), 3.69 (t, 4H,morpholine O(CH_2)$_2$), 5.15 (s, 2H, -N-CH_2), 7.2-7.3 (m, 5H, Ar-H), 7.38 (m, 5H, Ar-H), 10.1 (s, 1H, -N=CH). m/z: 464.2 [M^++1].

1-Piperidinomethyl-3-phenyl -4-(3-phenyl-4-sydnolidene) amino-5-mercapto-1, 2, 4-triazoles-5-thiones **(4c)**
IR (KBr) γ/cm^{-1}: 1318 (C=S), 1498 (C=C), 1584 (C=N), 1718 (C=O), 2934 (C-H), 2984 (Ar-H).^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 1.28 (t, 2H, CH_2, piperidine), 1.40-1.44 (m, 4H

piperidine), 2.60 (t, 4H, piperidine), 5.18 (s, 2H, N-CH_2-N), 7.20-7.28 (m, 5H, Ar-H), 7.34-7.38 (m, 5H Ar-H), 10.18 (s, 1H, -N=CH). m/z: 462.4 [M^++1].

1-p-Chloroanilinomethyl-3-phenyl -4-(3-p-tolyl-4-sydnolidene) amino-5-mercapto-1, 2, 4-triazoles-5-thiones **(4d)**
IR (KBr) γ/cm^{-1}: 1216 (C=S), 1560 (C=C), 1578 (C=N), 1718 (C=O), 2934 (C-H), 2976 (Ar-H), 3174 (N-H). ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 2.47 (s, 3H, CH_3), 5.18 (s, 2H, N-CH_2-N), 5.88 (s, 1H, N-H), 6.9 (d, 2H, J=8.2 Hz, meta protons of p-chlorophenyl), 7.2 (d, 2H, J=8.26Hz, ortho protons of p-chlorophenyl), 7.32 (d, 2H, J=7.7 Hz, meta protons of p-tolyl), 7.48 (d, 2H, J=7.76 Hz ortho protons of p-tolyl), 7.22-7.46 (m, 5H, Ar-H),10.12 (s, 1H, -N=CH). m/z: 518/520 [M^++1] [M^++3].

1-Morpholinomethyl-3-phenyl -4-(3-p-tolyl-4-sydnolidene) amino-5-mercapto-1, 2, 4-triazoles-5-thiones **(4e)**
IR (KBr) γ/cm^{-1}: 1318 (C=S), 1545 (C=C), 1581 (C=N), 1722 (C=O), 2938 (C-H), 2978 (Ar-H). ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 2.44 (s, 3H, CH_3), 2.64 (t, 4H, morpholine N$(CH_2)_2$), 3.68 (t, 4H, morpholine O$(CH_2)_2$), δ, 5.12 (s, 2H, N-CH_2-N), 7.28 (d, 2H, J=7.72 Hz, meta protons of p-tolyl), 7.38 (d, 2H, J=7.76Hz, ortho protons of p-tolyl), 7.42-7.5 (m, 5H, Ar-H), 10.12 (s, 1H, -N=CH). m/z: 477.4 [M^++1].

1-Piperidinomethyl-3-phenyl -4-(3-p-tolyl-4-sydnolidene) amino-5-mercapto-1, 2, 4-triazoles-5-thiones **(4f)**
IR (KBr) γ/cm^{-1}: 1288 (C=S), 1511 (C=C), 1582 (C=N), 1708(C=O), 2942 (C-H), 2976 (Ar-H). ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 1.39-1.6 (m, 6H, piperidine), 2.46 (s, 3H, CH_3), 2.79 (t, 4H, piperidine), 5.16 (s, 2H, N-CH_2-N), 7.26 (d, 2H, J=7.3 Hz, meta protons of p-tolyl), 7.32 (d, 2H, J=7.34 Hz, ortho protons of p-tolyl), 7.4 -7.48(m, 5H, Ar-H), 10.30(s, 1H, -N=CH). m/z: 475.4 [M^++1].

1-p-Chloroanilinomethyl-3-p-chlorophenoxymethyll -4-(3-phenyl-4-sydnolidene) amino-5-mercapto-1, 2, 4- triazoles-5-thiones **(4g)**
IR (KBr) γ/cm^{-1}: 1232 (C=S), 1454 (C-O-C), 1514 (C=C), 1584 (C=N), 1714 (C=O), 2940 (C-H), 2976 (Ar-H). ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 5.1 (s, 2H, O-CH_2-), 5.20 (s, 2H, -N-CH_2-N), 5.9 (s, 1H, N-H), 6.98 (d, 2H, J=8.26 Hz, meta protons of p-chlorophenyl), 7.12 (d, 2H, J=8.28 Hz, ortho protons of p-chlorophenyl), 7.2-7.38 (m, 9H, Ar-H), 10.18 (s, 1H, -N=CH). m/z: 582.2/584/586 [M^++1]/ [M^++3]/ [M^++5].

1-Morpholinomethyl-3-p-chlorophenoxymethyll -4-(3-phenyl-4-sydnolidene) amino-5-mercapto-1, 2, 4- triazoles-5-thiones **(4h)**

IR (KBr) γ/cm^{-1}: 1233 (C=S), 1518 (C=C), 1574 (C=N), 1716 (C=O), 2948 (C-H), 2982 (Ar-H). ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 2.62 (t, 4H, morpholine N$(CH_2)_2$), 3.71 (t, 4H, morpholine O$(CH_2)_2$), 5.1 (s, 2H, O-CH_2-), 5.18 (s, 2H, N-CH_2-N), 7.18-7.26 (m, 5H, Ar-H), 7.36 (d, 2H, J=8.12 Hz, meta protons of p-chlorophenyl), 7.42 (d, 2H, J=8.18Hz ortho protons of p-chlorophenyl), 10.18 (s, 1H, -N=CH). m/z: 528 [M^++1]

1-Piperidinomethyl-3-p-chlorophenoxymethyll -4-(3-phenyl-4-sydnolidene) amino-5-mercapto-1, 2, 4- triazoles-5-thiones **(4i)**
IR (KBr) γ/cm^{-1}: 1238 (C=S), 1382 (C-O-C), 1516 (C=C), 1588 (C=N), 1718 (C=O), 2942 (C-H), 2984 (Ar-H). ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 1.39-1.6 (m, 6H, piperidino),

2.79 (t, 4H, piperidine), 5.08 (s, 2H, O-CH_2-), 5.16 (s, 2H, N-CH_2-N), 7.22-7.34 (m, 5H, Ar-H), 7.33 (d, 2H, J=8.18 Hz, meta protons of p-chlorophenyl), 7.39 (d, 2H, J=8.2 Hz, ortho protons of p-chlorophenyl), 10.08 (s, 1H, -N=CH). m/z: 526/528 [M^++1]/ [M^++3].

1-p-Chloroanilinomethyl-3-p-chlorophenoxymethyll -4-(3-p-tolyl-4-sydnolidene) amino-5-mercapto-1, 2, 4- triazoles-5-thiones **(4j)**
IR (KBr) γ/cm^{-1}: 1302 (C=S), 1348 (C-O-C), 1504 (C=C), 1578 (C=N), 1722 (C=O), 2962 (C-H), 2994 (Ar-H), 3164 (N-H). ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 2.46 (s, 3H, CH_3), 5.12 (s, 2H, O-CH_2-), 5.18 (s, 2H, N-CH_2-N), 6.02 (s, 1H, NH), 6.98 (d, 2H, J=7.2 Hz, meta protons of p-chlorophenyl), 7.22 (d, 2H, J=7.28Hz ortho protons of p-chlorophenyl), 7.28 (d, 2H, J=8.1 Hz, meta protons of p-tolyl), 7.36 (d, 2H, J=8.18 Hz, ortho protons of p-tolyl), 7.38-7.46 (m, 4H, Ar-H), 10.10 (s, 1H, -N=CH). m/z: 583/585/587 [M^++1]/ [M^++3]/ [M^++5]

1-Morpholinomethyl-3-p-chlorophenoxymethyll -4-(3-p-tolyl-4-sydnolidene) amino-5-mercapto-1, 2, 4- triazoles-5-thiones **(4k)**
IR (KBr) γ/cm^{-1}: 1312 (C=S), 1354 (C-O-C), 1512 (C=C), 1574 (C=N), 1728 (C=O), 2966 (C-H), 2984 (Ar-H), 3124 (N-H). ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 2.46 (s, 3H, CH_3), 2.64 (t, 4H morpholine N(CH_2)$_2$), 3.74 (t, 4H, morpholine O(CH_2)$_2$), 5.13 (s, 2H, O-CH_2-), δ, 5.18 (s, 2H, N-CH_2-N), 7.18 (d, 2H, J=8.12 Hz, meta protons of p-tolyl), 7.32 (d, 2H, J=8.16 Hz, ortho protons of p-tolyl),7.32 (d, 2H, J=7.62 Hz, meta protons of p-chlorophenyl), 7.42 (d, 2H, J=7.68 Hz, ortho protons of p-chlorophenyl), 10.11 (s, 1H, -N=CH). m/z : 542/544 [M^++1]/ [M^++3].

1-Piperidinomethyl-3-p-chlorophenoxymethyll -4-(3-p-tolyl-4-sydnolidene) amino-5-mercapto-1, 2, 4- triazoles-5-thiones **(4l)**
IR (KBr) γ/cm^{-1}: 1312 (C=S), 1354 (C-O-C), 1514 (C=C), 1565 (C=N), 1730 (C=O), 2972 (C-H), 2988 (Ar-H), 3184 (N-H). ^{1}H-NMR (300MHz); solvent $CDCl_3$: δ, 2.46 (s, 3H CH_3), 1.4-1.62 (m, 6H, piperidino), 2.8 (t, 4H, piperidino), 5.08 (s, 2H, OCH_2), 5.18 (s, 2H, N-CH_2-N), 7.06 (d, 2H, J=7.4 Hz, meta protons of p-tolyl), 7.24 (d, 2H, J=7.48 Hz, ortho protons of p-tolyl), 7.38 (d, 2H, J=8.1 Hz, meta protons of p-chlorophenyl), 7.46 (d, 2H, J=8.18 Hz, ortho protons of p-chlorophenyl), 10.11 (s, 1H, -N=CH). m/z: 540/542 [M^++1]/ [M^++3].

Table I- Characterization data 0f 3-substituted-4-(3-aryl-4-sydnolidene) amino 5-mercapto-1,2,4-triazoles(Schiff bases) (3)

Compound No	R_1	R	Yield (%) MP(^{0}C)	Molecular formula	Colour and Crystal nature	Analysis % found (Calc)		
						C	H	N
3a	C_6H_5	H	78[b] 215-217	$C_{17}H_{12}N_6O_2S$	Yellow shining crystals	56.01 (56.04)	3.24 (3.29)	23.07 (23.07)
3b	C_6H_5	CH_3	80[a] 235-236	$C_{18}H_{14}N_6O_2S$	Pale yellow crystals	57.15 (57.14)	3.72 (3.70)	22.20 (22.22)
3c	P-Cl-C_6H_4-OCH_2	H	68[b] 208-210	$C_{18}H_{13}ClN_6O_3S$	Yellow crystals	50.41 (50.41)	3.01 (3.03)	19.60 (19.61)

3d	p-Cl-C_6H_4-OCH_2	CH_3	68[b] 216-218	$C_{19}H_{15}ClN_6O_3S$	Yellow Shining crystals	51.54 (51.53)	3.35 (3.39)	19.01 (18.99)

Solvent for recrystallization (a) EtOH+ Dioxane (b) EtOH + DMF

Table II- Characterization data of 1-substituted-aminomethyl-3-substituted -4-(3-aryl-4-sydnolidene) amino-1,2,4-triazol-5-thiones (Mannich bases) (4)

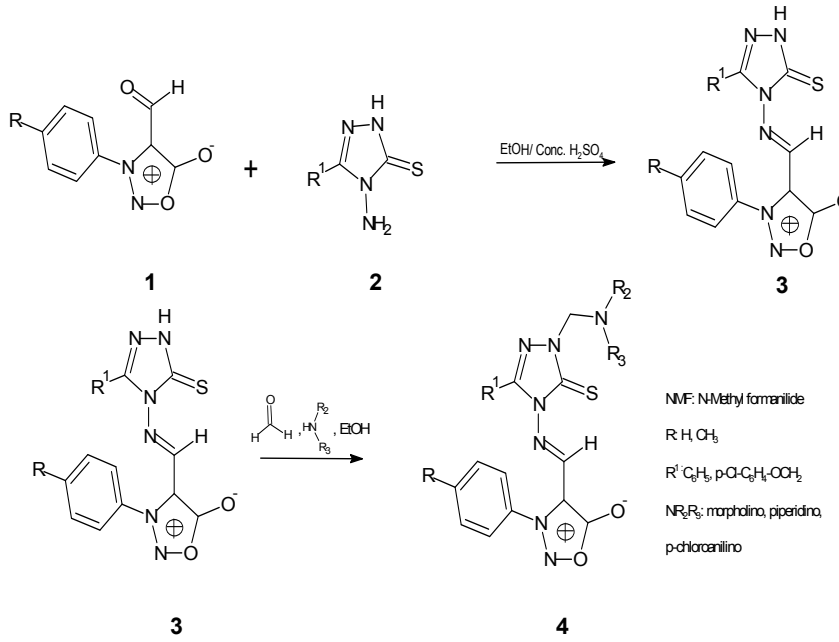
Compound No	R_1	R	NR_2R_3	Yield (%) MP(^{0}C)	Molecular formula	Colour and Crystal nature	Analysis % found (Calc)		
							C	H	N
4a	C_6H_5	H	p-Chloro anilino	70[a] 202-204	$C_{24}H_{18}ClN_7O_2S$	Yellow crystals	57.18 (57.21)	3.60 (3.58)	19.47 (19.47)
4b	C_6H_5	H	Morpholino	62[a] 176-178	$C_{22}H_{21}N_7O_3S$	Yellow Shining crystals	57.02 (57.02)	4.55 (4.54)	21.15 (21.17)
4c	C_6H_5	H	Piperidino	63[a] 182-183	$C_{23}H_{23}N_7O_2S$	Yellow crystals	56.89 (56.87)	5.01 (4.99)	21.20 (21.26)
4d	C_6H_5	CH_3	p-Chloro anilino	69[a] 180-182	$C_{25}H_{20}ClN_7O_2S$	Yellow Shining crystals	57.98 (57.98)	3.88 (3.86)	18.95 (18.94)
4e	C_6H_5	CH_3	Morpholino	71[a] 190-192	$C_{23}H_{23}N_7O_3S$	Pale yellow crystals	57.83 (57.86)	4.87 (4.82)	20.53 (20.54)
4f	C_6H_5	CH_3	Piperidino	63[b] 182-184	$C_{24}H_{25}N_7O_2S$	Yellow Shining crystals	60.63 (60.63)	5.30 (5.26)	20.62 (20.63)
4g	P-Cl-C_6H_4-OCH_2	H	p-Chloro anilino	56[a] 178-180	$C_{25}H_{19}Cl_2N_7O_3S$	Yellow crystals	52.80 (52.83)	3.32 (3.35)	17.23 (17.26)
4h	P-Cl-C_6H_4-OCH_2	H	Morpholino	58[a] 148-150	$C_{23}H_{22}ClN_7O_4S$	Yellow flakes	52.32 (52.33)	4.19 (4.17)	18.60 (18.58)

4i	P-Cl-C_6H_4-OCH_2	H	Piperidino	62[b] 186-188	$C_{24}H_{24}ClN_7O_3S$	Yellow flakes	54.89 (54.81)	5.01 (4.57)	18.40 (18.65)
4j	P-Cl-C_6H_4-OCH_2	CH_3	p-Chloro anilino	70[a] 190-192	$C_{26}H_{21}Cl_2N_7O_3S$	Yellow flakes	53.58 (53.62)	3.68 (3.61)	16.95 (16.85)
4k	P-Cl-C_6H_4-OCH_2	CH_3	Morpholino	65[a] 180-182	$C_{24}H_{24}ClN_7O_4S$	Yellow flakes	53.23 (53.19)	4.37 (4.43)	18.13 (18.09)
4l	P-Cl-C_6H_4-OCH_2	CH_3	Piperidino	63[b] 186-188	$C_{25}H_{26}ClN_7O_3S$	Yellow flakes	55.63 (55.61)	4.75 (4.82)	18.10 (18.17)

Solvent of Recrystallization: (a) EtOH (b) EtOH+Dioxane

3. RESULT AND DISCUSSIONS

Mannich bases **4** were prepared by the reaction of Schiff bases **3**, formaldehyde (40%) and suitable amines (either primary or secondary amine) in a mixture of ethanol + dioxane medium as given in scheme 1. P-Cholro aniline was the primary amine employed, piperidine and morpholine are the secondary amines employed in the preparation of the Mannich bases. These amines were obtained commercially and were used after purification either by crystallisation or by distillation. Schiff bases were prepared by the condensation of 3-substituted-4-amino-5-mercapto-1,2,4-triazoles **2** carrying aryl and aryloxy methyl substituents at position 3 with 3-aryl-4-formyl-sydnones **1** in presence of catalytic amount of concentrated sufuric acid in ethanol medium.The characterization data of Schiff bases **3** and Mannich bases **4** are given in table I table and II respectively. It is interesting to note that the reaction is highly regioselective and furnishes only N-Mannich base and none of the S-Mannnich derivatives, although the Schiff bases **3** can exist in thiol-thione tautomeric form.The result of elemental analysis agrees with the theoretical values within the limits of experimental error.



Scheme 1. Synthetic route of the compound 4

Pharmacology

*Anti-inflammatory activity***:**

The anti-inflammatory activity studies were carried out according to the method of Winter *et al.* [XVI] using ibuprofen as standard drug. Groups of five albino rats of either sex weighing about 100-200 g were used. Formalin (6%, 0.1 ml) was injected into the plantar surface of the rat's hind paw 30 min after administration of the test compounds (20 mg/kg). Paw volume was measured after 1, 3 and 5 h. Results are shown in Table **III**.

*Analgesic activity***:**

Acetic acid induced writhing test in mice was carried out employing the method of Collier *et al*[XVII]. Albino mice weighing 20-25 g were used for this test. A day prior to drug testing, these mice were given an injection of 0.6% acetic acid (1 ml/100g) intraperitonially, only those which gave positive writhings episodes were selected. The number of writhing movement exhibited by each mouse over a period of 20 minutes was recorded. The selected mice were then divided into 6 groups containing 5 animals. The following day vehicles/drug was administered intraperitonially to the mice. After half an hour an intraperitonial injection of 0.6% acetic acid was given and number of writhes in the treated and control groups was recorded. The % protection was calculated using the formula

$$\% \text{ protection} = 100 - \left(\frac{\text{Total writhes in treated mice}}{\text{Total writhes in control mice}} \right) \times 100$$

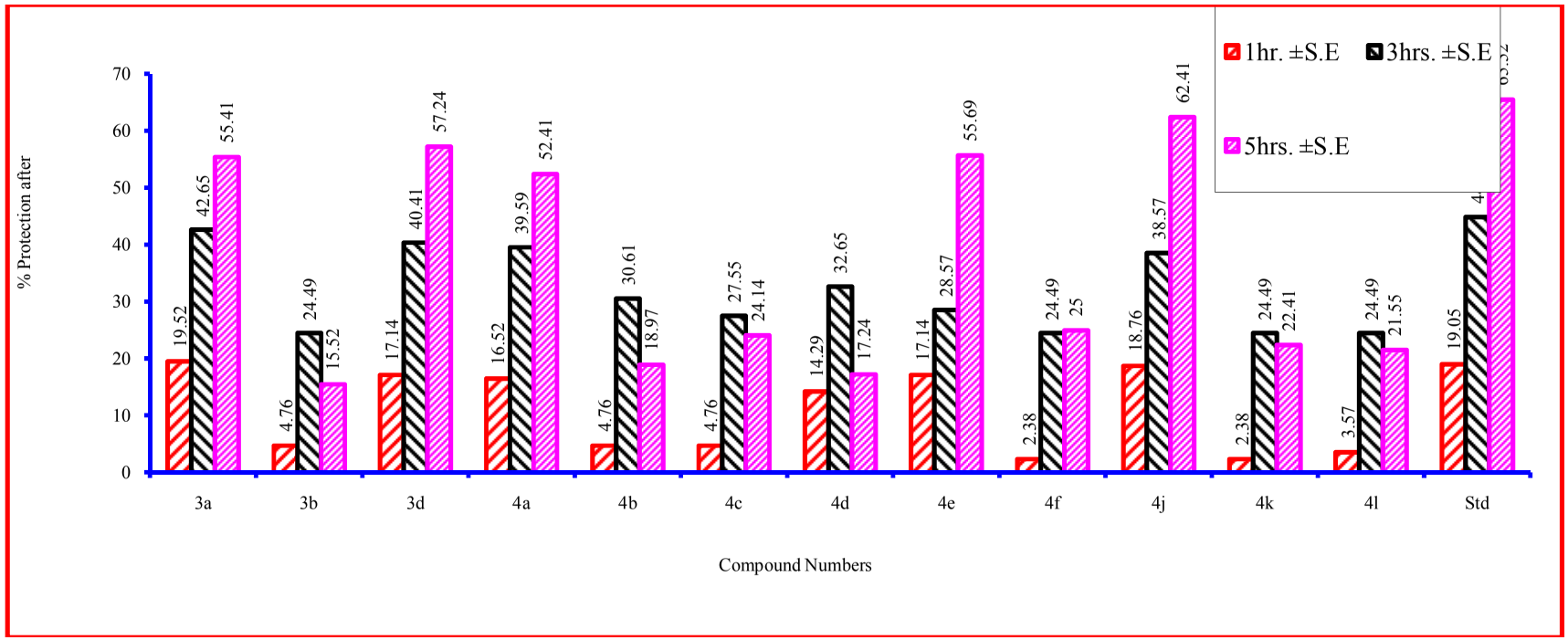
The results are given in the Table **IV**. Ibuprofen was employed as the standard.

CNS Depressant activity[XVIII]*:*

Thirty healthy albino rats of body weight 100-200 g were selected and kept them for 8 hours fasting. These fasted animals were made into 6 groups randomly, each of 5 animals. Group 1 animals received standard drug pentobarbitone 35 mg/kg body weight intraperitonially. All other groups of animals received test compounds 35 mg/kg intraperitonially along with pentabarbitone sodium. The time of onset of action was noted as the animal losses its

wrighting reflux i.e. falls sleep. The time of recovery from sleep is noted as it turns to recover its normal posture. The onset and duration of action is calculated. The results are given in Table **V**.

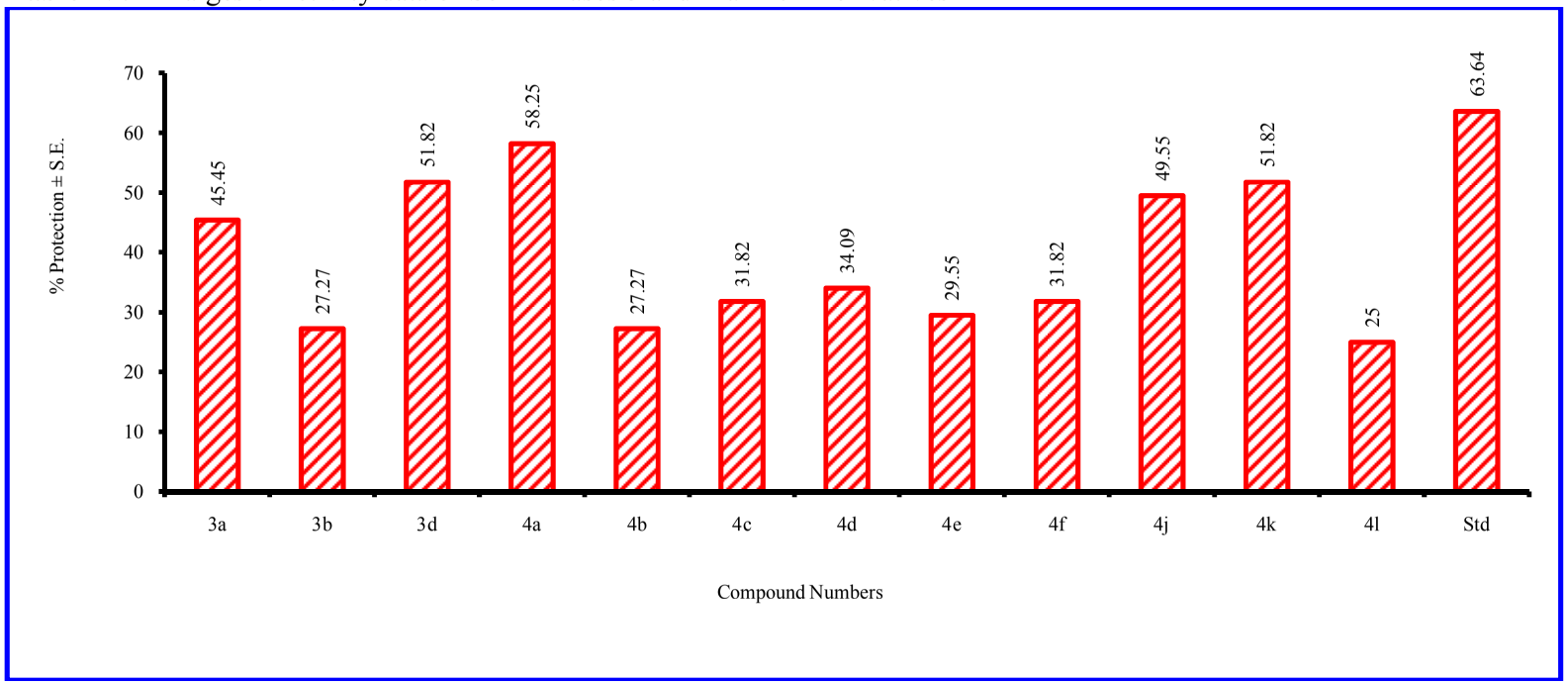
Table III : Anti-inflammatory activity data of Schiff Bases **3** and Mannich Derivatives **4**



Index for anti-inflammatory activity:

Model	: Acute anti-inflammatory
Method	: Formalin induced oedema test
Animals	: Albino rats (100-200g)
No. of animals per group	: 05
Route of administration	: Intra-peritoneally
Standard drug	: Ibuprofen
Dose	: 20mg/kg body weight
Average body weight of animals	: 150g
Control	: 2% acacia mucilage

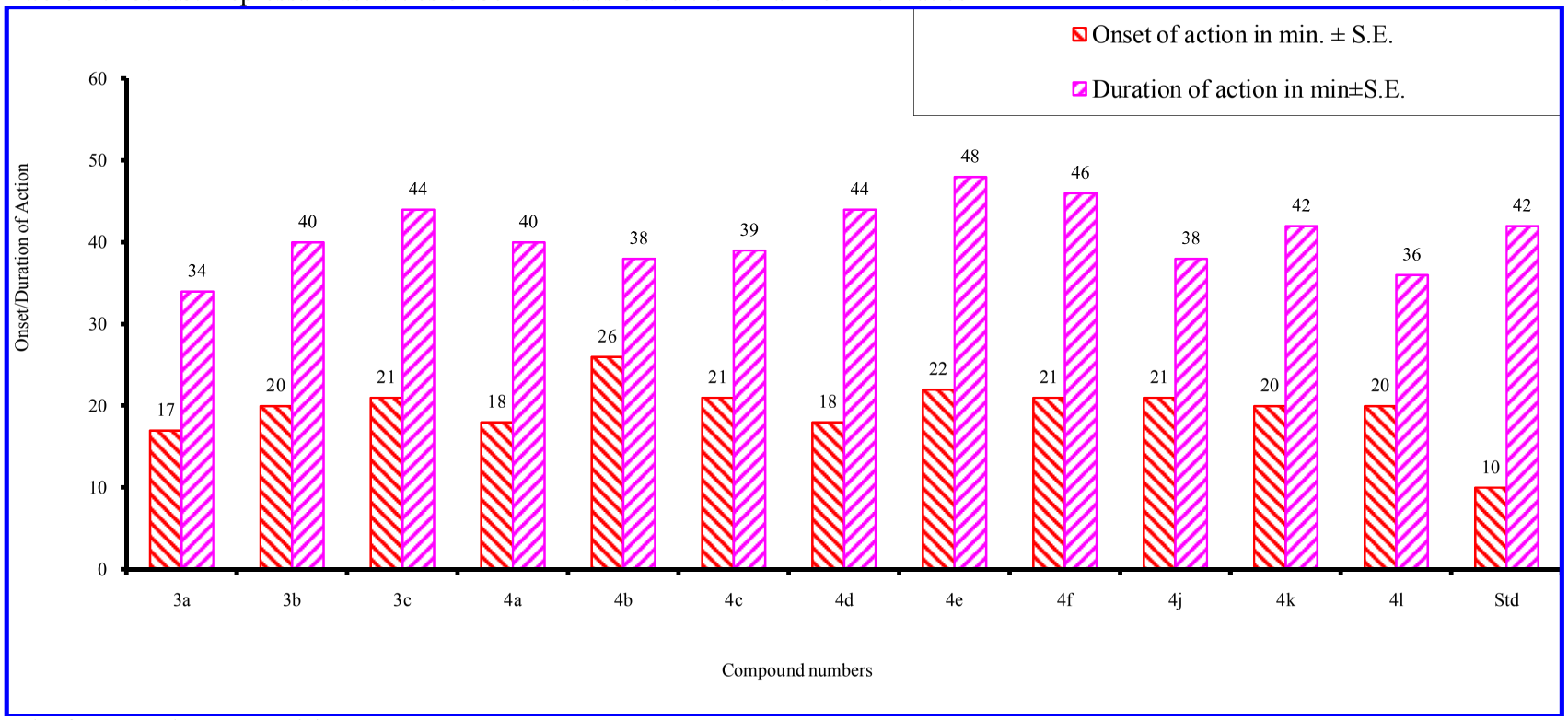
Table IV:- Analgesic Activity data of Schiff Bases **3** and Mannich Derivatives **4**



Index for analgesic activity data:

Method	: Acetic acid induced writhing, (acetic acid-0.6% concentration)
Animals	: Albino mice (20-25g)
No. of animals per group	: 05
Route of administration	: Intra-peritoneally
Standard drug	: Ibuprofen
Dose	: 100mg/kg body weight

Table V:- C.N.S. Depressant activities of Schiff Bases **3** and their Mannich Derivaties **4**



Index for C.N.S. depressant activity:

Model : Effect of the drug on pentabarbitone induced sleep
Animals : Albino rats (100-200g)
No. Of animals per group : 05
Route of administration : Intraperitoneally
Standard drug : Pentobarbitone (35mg/kg) intraperitoneally
Test compounds : 35mg/kg intraperitoneally
S.E. : Standard Error.

4. CONCLUSION

In the present study we synthesized series of Schiff and Mannich base and evaluated for their biological activities. Few compounds from this series were screened for their anti-inflammatory, analgesic and C.N.S. depressant activity. Among the tested compounds **3a**, **3d**, **4a**, **4e** and **4j** showed significant anti-inflammatory activity comparable with that of standard drug ibuprofen. **3a**, **4a**, **4j** and **4k** showed promising analgesic activity. Compounds containing chlorine substituents showed significant activity. Most of the compounds tested showed promising C.N.S. depressant activity comparable with that of standard drug pentobarbitone.

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