Original Research Paper

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Synthesis and Evaluation of Heterocyclic Derivatives of Morpholino-N-Acetyl Indoles for Central Nervous System Depressant Activity

Chemistry

KEYWORDS : Morpholine, imino indole, chloroacetyl chloride, Chlorpromazine hydrochloride, CNS activity.

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ABSTRACT

In the present work, 2-oxo-3[4`-p (subst/unsubst)-phenyl-2`-thiazolyl/oxazolyl] morpholino-N-acetyl indoles were synthesized. The different heterocyclic moieties were condensed with isatin in ethanol containing few drops of glacial acetic acid which were converted into various Thiazolyl/oxazolyl imino indoles. The imino indoles were condensed with chloro acetyl chloride in K2CO3 which were converted to N-chloro acetyl indole derivatives which on subsequent treatment with morpholino in benzene were converted to title compound. The structures of the synthesized compounds were characterized on the basis of IR and HNMR spectral data. Among all the synthesized compounds few selected compounds were screened for their CNS activity. Chlorpromazine hydrochloride is employed as a reference standard. From the results it is concluded that, synthesized compounds show more depressant activity than reference standard.

INTRODUCTION

The drug which decreases the activity of some parts of brains or spinal cord is called central nervous depressants. CNS depressants, sometimes referred to as sedatives and tranquilizers are substances that can slow brain activity. CNS depressants slow normal brain function. CNS depressants can be divided into two groups, based on their chemistry and pharmacology:

Barbiturates, such as mephobarbital (Mebaral) and pentobarbital sodium (Nembutal), which are used for the treatment of tension, sleep disorders as well as anxiety

Benzodiazepines, such as diazepam, chlordiazepoxide HCl, and alprazolam, are used for the treatment of anxiety, acute stress and panic attacks.

Various indole derivatives are reported to be effective in CNS disorders such as convulsion and depression. Substituted 1,3,4 oxadiazoles derivatives are reported to show broad spectrum of biological activities viz. bactericidal, fungicidal, herbicidal, antiviral and CNS depressant. Thiazolidinones are used as sedatives, hypnotics, antipasmodic or anticonvulsant. Christopher B. Chapleo *et al*. synthesized a series of 2-aryl-5-hydrazino-l,3,4-thiadiazole derivatives and evaluated them for anticonvulsant activity[1].

Person et-al (1980) reported CNS depressant activity in asymmetric triazines. Rao and Mittra (1978) reported CNS activity in various pyrazole and pyrazolone derivatives. Indoles and Indolinones have been shown to possess a wide spectrum of biological activities viz. anti-microbial, fungicidal, anti-inflammatory and CNS stimulating. The literature survey shows that indoline derivatives which have a wide range of biological activities such as antimicrobial, anti-inflammatory, antihistamine, antioxidant, anti-proliferative and antidepressants.

A series of 3-substituted 5-methoxycarbonyl-5-methoxycarbonylmethyl-1,4,2-dioxazoles was prepared by Ned D. Heinde et all for pharmacological screening as CNS depressant activity.[3]5-(2-Aminoethyl)-2-oxazolidinones with central nervous system depressant and anti-inflammatory activity were reported by Welstead WJ et al in 1973[4]. 5-(2-substituted alkyl)-2-oxazolidinones[5] & new oxaza heterocyclic amides[6], were synthesized by Filder etal & Pifferi et al & reported to possess CNS depressants activity. Compound with 4-OH, 3-OCH3 substitution on phenyl ring and hydrogen group on thiazolidine ring showed more promising CNS depressant reported by N.Sunitha et. Al.[7]
Sudheer Babu I and Selvakumar S co-relates structural activity relationship studies on synthesized compounds ,1-ortho phenyl carboxylic acid substituted and 1- phenyl substituted benzimidazolyl isoindolines, which showed good CNS depressant activity[8]. Raghunandan Nerella *et al* synthesized a series of new 1-NSubstituted amino methyl-3-(3-phenyl quinazolin-4-one-methylene- 2-yl) indolin-2-one showed CNS depression activity[9].

A survey of literature reveals that benzotriazoles derivatives possess immense biological properties such as anti-inflammatory, analgesic, anti-bacterial, hypertensive and CNS depressant activity. 1,2,4 triazole derivatives have exhibited valuable pharmacological activities like anticonvulsant and anti-depressant. K. P. Harish et al. synthesized a series of 2-amino-5-sulphanyl-1,3,4-thiadiazole derivatives and evaluated for the anticonvulsant activity[2]. The synthesized compounds exhibited excellent anticonvulsant activity in comparison to the reference drugs[2]. Saxena and Khan (1989) reported CNS depressant activity in quinazolone derivatives. John (1982 and 1986) reported that quinazoline and its synthetic analogue exhibit biological activities like anticonvulsant, anti-depressant & CNS stimulants.

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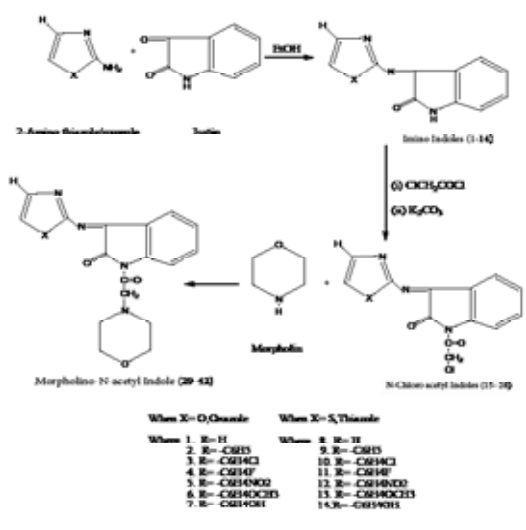
Bethi Srinivas *et al.* synthesized a series of isatin derivatives containing 1, 2, 3, 4- tetrahydrocarbazole moiety, the synthesized compound exhibited central nervous system depression in the mice.[10] 3-(1H-benzimidazol-2-yl amino) 2-phenyl-1,3-thiazolidin-4-one as potential CNS depressant

agents were reported by Ganesh etal.[11] Poonam Singh et al synthesized substituted diphenyl- 1,3,4-oxadiazole derivatives for central nervous system depressant activity and concluded that introduction of electron withdrawing group at C2& C5 position of the oxadiazole nucleus increases the pharmacological activity[12].[1-(thiophen-2-yl] ethylidene] hydrazine and 4, 4′-(hydrazine-1,2- diylidenedimethylylidene) bis (N,N-dimethyl aniline) were synthesized and screened for CNS depressant activity by P. Deivanayagam et al[13]. 5-amino-1,3,4-thiadiazole-2-thiol were reported as anticonvulsant activity by yusuf et al[14].

Rajesh Sharma et al. reported 2-(2-(3-(4-chlorophenyl)-6-oxo-5,6- dihydropyridazin- 1(4H) yl)acetyl)hydrazine carbothioamide and 2-((5-amino-1,3,4-thiadiazol-2-yl) methyl)-6-(4- chlorophenyl)-4,5- dihydropyridazin-3(2H)-one derivatives and found to possess anticonvulsant activity.[15] Indulatha VN et al synthesized Novel N-4′-oxo-2′-(substituted phenyl)-thiazolidin-3′-yl]-3-carboxamido-2H-chromen-2-one and evaluated for their anticonvulsant activity[16]. Xinghua Zhen et al., synthesized 2-(5-methyl-2,3-dioxoindolin-1-yl) acetamide derivatives and reported for their anticonvulsant activity[17] .

K. Swathi *et al.* carried out synthesis and sedative-hypnotic activity of novel series of isatin hydrazone and isatin thiosemicarbazone derivatives by using potentiation of pentobarbitone induced Narcosis method against standard drug diazepam (50mg/kg) [18].

Lots of work has been done on thiazole & oxazole nucleus with potential biological activities. Various Indole derivatives are reported to possess CNS depressant activity. Keeping all these views and literature survey attempts were made to synthesize various N-acetyl indole derivatives and screened for CNS depressant activity. (Scheme-1)



(Scheme-I)

MATERIALS AND METHODS

All the melting points were determined in open capillary tubes. IR spectra were recorded in solid state using KBr pellet method. The spectra were recorded on Perkin Elmer FT-IR spectrophotometer (model RX-1). The PMR spectra were recorded in DMSO-d6 solvent at room temperature using TMS as reference compound. The spectra were recorded on Perkin Elmer Model 32 NMR spectrometer at 300MHz at CDRI Lucknow.

The reactions were monitored by TLC. The required 2-Amino-4-[p-subst/unsubst] phenyl thiazoles / oxazoles were prepared by know method. Procedure for one compound of each step has been described in sequel.

Synthesis of 2-Amino – Oxazole

A solution of 60 gm of urea in 200 ml of warm water is placed in 500 ml three necked flask equipped with dropping funnel ,mechanical stirrer and reflux condenser.143 gm of α,β-dichloroethyl ether is added and the mixture is heated under gentle reflux with stirring for 2 hrs. As the reaction proceeds, the two layers gradually merge. To the cold solution, sufficient solid NaOH is added to liberate 2-Amino oxazole from its salt. Ether is added to dissolve the product and ether is evaporated.2-Amino oxazole is recrystallized from ethanol.

M.P.: 90- 95^{0}C.

IR (KBr): 1255 cm^{-1} (due to C-N), 1475 - 1453 cm^{-1}(due to C=N), 3065-3005 cm^{-1} (due to C-H), 1565-1558 cm^{-1} (due to N=C-O), 3300-3135 cm^{-1} (due to N-H),

PMR: δ 6.7 (s, 1H, due to -CH), δ 7.2 (s, 1H, due to -CH), δ 5.12 (br, s, 2H, due to NH_2).

Synthesis of 2-Amino-4-phenyl Oxazole:

In a round bottom flask, add 2-bromo-1-phenylethanone (1.0 m mol), urea (1.0 m mol) and PEG (0.5mL) under reflux until the completion of reaction (monitored by TLC). The resultant compound was washed with water (4mL) then extracted with ethyl acetate (3 X 15 ml). The organic phase was separated & passed through anhydrous sodium sulphate, and filtered. The excess solvent was removed under vacuum. The crude mixture was purified by using standard silica gel column chromatography in ethyl acetate & petroleum ether in the ratio of 1:1. After extraction with ethyl acetate, H2O and PEG 400 were removed by heating mixture to its boiling point.

B.P: 113-115^{0}C

IR (KBr): 1255 cm^{-1} (due to C-N), 1475 - 1453 cm^{-1}(due to C=N), 3065-3005 cm^{-1} (due to C-H), 1565-1558 cm^{-1} (due to N=C-O), 3300-3135 cm^{-1} (due to N-H), 1155-1103 cm^{-1} (due to C-O-C)

NMR: (300 MHz, CDCl3): δ 7.52–7.47 (m, 2H, ArH), 7.33–7.28 (m, 2H, ArH), 7.09 (m, 1H, ArH), 6.74 (s, 1H, oxazole), 5.17 (br s, 2H, NH2)

Similarly, 2-Amino-4-p-chloro/ fluoro/ nitro /methoxy/ hydroxy phenyl oxazoles were prepared.[37-39]

Synthesis of 2-Amino – Thiazole

A solution of 76 gm of thiourea in 200 ml of warm water is placed in 500ml three necked flask equipped with dropping funnel ,mechanical stirrer and reflux condenser.143 gm of α,β-dichloroethyl ether is added and the mixture is heated under gentle reflux with stirring for 2 hrs. As the reaction proceeds, the two layers gradually merge. To the cold solution, sufficient solid NaOH is added to liberate 2-Amino Thiazole from its salt. Ether is added to dissolve the product and ether is evaporated.2-Amino Thiazole is recrystallized from ethanol.

M.P.: 90- 91^{0}C.

IR (KBr): 1255 cm^{-1} (due to C-N), 694 cm^{-1} (due to C-S-C), 1615 & 1535 cm^{-1}(due to C=N)

PMR: δ 6.6 (s, 1H, due to -CH), δ 7.1 (s, 1H, due to -CH), δ 11.4 (d, 2H).

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Synthesis of 2-Amino-4-phenyl Thiazole
A mixture of acetophenone (12.0gm, 0.1mol), thiourea (15.2gm, 0.2mol) and iodine (25.4gm, 0.1mol) was heated for 10 hours on a steam bath. The crude reaction mixture was cooled and repeatedly extracted with ether to remove unreacted acetophenone and iodine. The residue was then dissolved in hot water and filtered to remove sulphur and other impurities. The solution was then moderately cooled and made alkaline with conc. Ammonia.2-amino-4-phenyl thiazole, thus precipitated was collected and recrystallized from diluted ethanol as long colorless needles.

M.P.: 149^{0}C.
IR (KBr): 1255 cm^{-1} (due to C-N), 694 cm^{-1} (due to C-S-C), 1615 & 1535 cm^{-1}(due to C=N)

PMR: δ 6.6 (s, 1H, due to -CH), δ 7.5 (m, 5H, Aromatic), δ 11.35 (d, 2H,-NH_2).

Synthesis of 2-oxo-3-[Thiazolyl] imino indoles [1-14]
An equimolar quantity of isatin and 2-amino thiazole in ethanol containing traces amount of glacial acetic acid was refluxed on a water bath for 4 hours. The solid which separated on cooling was filtered and re-crystallize from ethanol.

Yield = 72%
M.P = 119°-121°C

IR (KBr): 3440 cm^{-1} (due to –NH str.), 1690 cm^{-1} (due to C=O), 1252 – 1225 cm^{-1} (due to C-N), 1525 cm^{-1} (due to C=N), 1600- 1465 cm^{-1} (due to C=C), 690 cm^{-1} (due to C-S-C).

PMR: δ 7.0 – 7.75 (m, 6H, due to Ar-H), δ 8.0-8.2 (s, 1H, due to -NH), 2.5-2.7 (s, 1H due to –NH).

Similarly various 2-oxo-3-[subst/unsubst Thiazolyl /oxazolyl] imino indoles were synthesized by using similar reaction procedure.

Synthesis of 2-oxo-3-[Thiazolyl]-N- chloro acetyl indoles [15 - 28]

To the compound [1-14], 0.005 mol add drop wise chloro acetyl chloride in K_2CO_3 using benzene as a solvent and refluxed on water bath for 8 hours. The resulting solid which on cooling was filtered and recrystallize from ethanol.

Yield = 65%
M.P = 126°-128°C

IR (KBr): 1690 & 1715 cm^{-1} (due to C=O), 1252 – 1225 cm^{-1} (due to C-N), 1525 cm^{-1} (due to C=N), 1600- 1465 cm^{-1} (due to C=C), 690 cm^{-1} (due to C-S-C), 740 cm^{-1} (due to C-Cl)

PMR: δ 7.0 – 7.8 (6H, m, due to Ar-H), δ 4.1- 4.32 (2H, d, due to –CH_2-Cl), 2.65-2.74 (1H,s, due to -NH)

Similarly, various 2-oxo-3-[subst/unsubst Thiazolyl / oxazolyl]-N- chloro acetyl indoles were synthesized by using similar reaction.

Synthesis of 2-oxo-3-[Thiazolyl] Morpholino-N-Acetyl Indoles
To the compound [15-28] is treated with equimolar quantities of morpholino in benzene on water bath for 10 hours. The resulting solid so obtained was re-crystallized from EtOH.
Yield = 55%
M.P = 135°-137°C

IR (KBr): 1715 cm^{-1} (due to C=O), 1680 – 1620 cm^{-1} (due to C=N), 1250 – 1220 cm^{-1} (due to C-N), 1120 cm^{-1} (due to CH_2-O-CH_2), 1605-1615 cm^{-1} (due to –CO-N).

PMR: δ 7.0 – 7.8 (6H, m, due to Ar-H), δ 2.0- 2.27 (2H, d, due to –CH_2-N), 2.65-2.74 (1H, s, due to -NH), 2.27-3.67 (8H, m, due to –CH_2).

Similarly, 2-oxo-3-[subst/unsubst Thiazolyl / oxazolyl] Morpholino-N- Acetyl indoles were synthesized by using similar reaction procedure. The analytical data of all the synthesized compounds are incorporated in Table 1 respectively.

Table-1
Physical Data of Synthesized Compounds

Comp'd No.	Nature of R	Molecular Formula	MP°(C)	Yield (%)
1	2-Amino- Thiazole	$C_{11}H_7N_3SO$	119 - 121	72
2	2-Amino-4-phenyl Thiazole	$C_{17}H_{11}N_3SO$	125 - 127	75
3	2-Amino-4-(p-chloro) phenyl Thiazole	$C_{17}H_{10}N_3$ SOCl	123 -125	69
4	2-Amino-4-(p-fluoro) phenyl Thiazole	$C_{17}H_{10}N_3SOF$	125-127	60
5	2-Amino-4-(p-nitro) phenyl Thiazole	$C_{17}H_{10}N_4SO_3$	129-131	63
6	2-Amino-4-(p-methoxy) phenyl Thiazole	$C_{18}H_{13}N_3SO_2$	134-136	68
7	2-Amino-4-(p-Hydroxy) phenyl Thiazole	$C_{17}H_{11}N_3SO_2$	132-134	70
8	2-Amino- oxazole	$C_{11}H_7N_3O_2$	110-112	67
9	2-Amino-4-phenyl oxazole	$C_{17}H_{11}N_3O_2$	115-117	75
10	2-Amino-4-(p-chloro) phenyl oxazole	$C_{17}H_{10}N_3O_2Cl$	121-123	62
11	2-Amino-4-(p-fluoro) phenyl oxazole	$C_{17}H_{10}N_3O_2F$	127-129	59
12	2-Amino-4-(p-nitro) phenyl oxazole	$C_{17}H_{10}N_4O_4$	123-125	69
13	2-Amino-4-(p-methoxy) phenyl oxazole	$C_{18}H_{13}N_3O_3$	127-129	73
14	2-Amino-4-(p-Hydroxy) phenyl oxazole	$C_{17}H_{11}N_3O_3$	130-132	60
15	2-Amino- Thiazole	$C_{13}H_8N_3SO_2Cl$	136-138	65
16	2-Amino-4-phenyl Thiazole	$C_{19}H_{12}N_3$ SO_2Cl	140-142	55

17	2-Amino-4-(p-chloro) phenyl Thiazole	$C_{19}H_{12}N_3SO_2Cl_2$	139-141	62
18	2-Amino-4-(p-fluoro) phenyl Thiazole	$C_{19}H_{12}N_3O_3Cl_2$	143-145	60
19	2-Amino-4-(p-nitro) phenyl Thiazole	$C_{19}H_{11}N_4O_4ClS$	147-149	53
20	2-Amino-4-(p-methoxy) phenyl Thiazole	$C_{20}H_{14}N_3SClO_3$	155-157	49
21	2-Amino-4-(p-Hydroxy) phenyl Thiazole	$C_{19}H_{12}N_3O_3ClS$	150-152	45
22	2-Amino- oxazole	$C_{13}H_8N_3O_3Cl$	138-140	52
23	2-Amino-4-phenyl oxazole	$C_{19}H_{12}N_3O_3Cl$	144-146	55
24	2-Amino-4-(p-chloro) phenyl oxazole	$C_{19}H_{12}N_3O_3Cl_2$	147-149	52
25	2-Amino-4-(p-fluoro) phenyl oxazole	$C_{19}H_{12}N_3O_3F_2$	138-140	54
26	2-Amino-4-(p-nitro) phenyl oxazole	$C_{19}H_{11}N_4O_5Cl$	155-157	50
27	2-Amino-4-(p-methoxy) phenyl oxazole	$C_{20}H_{14}N_3ClO_4$	150-152	55
28	2-Amino-4-(p-Hydroxy) phenyl oxazole	$C_{19}H_{12}N_3O_4Cl$	157-159	49
29	2-Amino- Thiazole	$C_{17}H_{16}N_4SO_3$	165-167	55
30	2-Amino-4-phenyl Thiazole	$C_{23}H_{20}N_4SO_3$	172-173	52
31	2-Amino-4-(p-chloro) phenyl Thiazole	$C_{23}H_{19}N_4SO_3Cl$	163-165	47
32	2-Amino-4-(p-fluoro) phenyl Thiazole	$C_{23}H_{19}N_4SO_3F$	169-171	50
33	2-Amino-4-(p-nitro) phenyl Thiazole	$C_{23}H_{19}N_5O_5S$	175- 177	45
34	2-Amino-4-(p-methoxy) phenyl Thiazole	$C_{24}H_{22}N_4O_4S$	169-171	42
35	2-Amino-4-(p-Hydroxy) phenyl Thiazole	$C_{23}H_{20}N_4O_4S$	179-181	46
36	2-Amino- oxazole	$C_{17}H_{16}N_4O_4$	163-165	48
37	2-Amino-4-phenyl oxazole	$C_{23}H_{20}N_4O_4$	189-191	50
38	2-Amino-4-(p-chloro) phenyl oxazole	$C_{23}H_{19}N_4O_4Cl$	183-185	42
39	2-Amino-4-(p-fluoro) phenyl oxazole	$C_{23}H_{19}N_4O_4F$	172-174	35
40	2-Amino-4-(p-nitro) phenyl oxazole	$C_{23}H_{19}N_5O_6$	175- 177	37
41	2-Amino-4-(p-methoxy) phenyl oxazole	$C_{24}H_{22}N_4O_5$	199-181	39
42	2-Amino-4-(p-Hydroxy) phenyl oxazole	$C_{23}H_{20}N_4O_5$	185-187	36

RESULTS AND DISCUSSIONS

Central Nervous system (CNS) Activity:

The 14 mice were used for pharmacological screenings. The CNS activity was studied by using mice through oral route using cannula insertion via mouth. The decrease in count in comparison to corresponding control was compared after 30 minutes by digital Actophotometer and was tabulated before and after drug administration. The mean % score for a group was plotted and chart for dose of drug (20mgm/kg) were drawn. The Pharmacological screening of the synthesized compounds and the effect of CNS activity in mice is summarized in Table 2- 3.

The mean value of corresponding control was compared with synthesized compounds and it shows more depressant activity than chlorpromazine hydrochloride. The synthesized compounds, showed average % Change in activity mean 59.90 % & against standard Chlorpromazine hydrochloride which showed average % Change in activity mean 67.17. The Pharmacological screening of standard reference is given in Table -1 & pharmacological screening of synthesized compounds is given in Table 3. Graph 1 for comparative study with standard drug and synthesized compounds, respectively. After 24 hours the used mice were showed normal behavior.

Table2: CNS Study of Chlorpromazine hydrochloride

Control Drug	Dose mg/kg	Activity after 30 minutes (in activity cage recorder)		
		Before treatment	After Treatment	% Change in activity
Chlorpromazine hydrochloride	20mg/kg	260	80	69.23
		300	100	66.66
		320	110	65.63
			Mean	67.17

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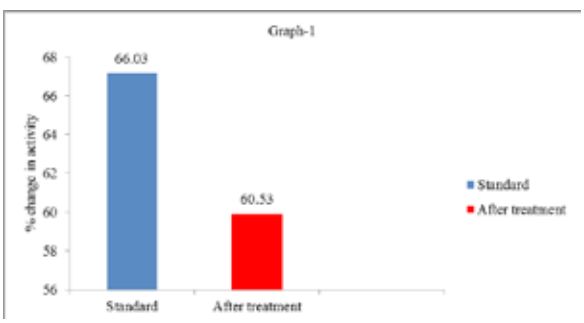
Table 3: CNS Study of 2-oxo-3- [subst / unsubst Thiazolyl /oxazolyl] - N- chloro acetyl indoles.

Compound No.	Dose mg/kg	Activity after 30 minutes (in activity cage recorder)		
		Before treatment	After Treatment	% Change in activity
29	20mg/kg	260	100	61.15
31		245	90	63.26
32		230	85	63.04
34		200	90	55.00
35		189	80	57.67
37		295	110	62.71
38		330	130	60.6
39		350	150	57.14
40		250	100	60.0
41		275	115	58.18
42		300	110	60.18
			Mean	59.90



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