Research Article

SYNTHESIS AND CNS ACTIVITY OF NEW INDOLE DERIVATIVES

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Accepted on: 14-12-2010; **Finalized on:** 22-03-2011.

ABSTRACT

Some new 1-N- Substituted amino methyl-3-(3-phenyl quinazolin-4-one-methylene-2-yl) indolin-2-ones(VIII) have been synthesized by subjecting an appropriate 3-(3-phenyl quinazolin-4-one methylene-2-yl) indolin-2-ones (VII) to mannich reaction with three different secondary amines viz. dicyclohexylamine, piperidine and morpholine in presence of formaldehyde and alcohol. Their chemical structures have been confirmed by IR, 1HNMR, MASS and by elemental analysis. All the synthesized compounds were screened for CNS activity. The gross behavioral studies of test compounds reveal that all the test compounds exhibited CNS depression in the mice. All the test compounds showed a decrease in Locomotor activity. Except VIIIb increased locomotor activity which is found to be not significant. Compounds VIIId, VIIIa, VIIIc and VIIg were next to compound VIIIe in the order of reduction of locomotor activity.

Keywords: Isatin, Quinazolinones, Locomotor activity, Gross behavioral studies.

INTRODUCTION

Indoles and its derivatives have occupied a unique place in the chemistry of nitrogen heterocyclic compounds, because of their varied biological properties. But earlier derivatives of indoles were known for their dyeing properties. Only after the twentieth century, a large number of naturally occurring compounds like alkaloids[1], were known to possess indole nucleus. During this period the recognization of plant growth hormone heteroauxin and the essential amino acid tryptophan as the derivatives of indole have been added stimulus to the research.

It is evident from literature that indole containing synthetic compounds and their derivatives are known to be associated with broad spectrum of biological activity like antipyretic activity, analgesic effect[2,3] anticonvulsant activity[4], few compounds were also reported as psychotropic agents[5], MAO inhibitors[6]. All the reported activities provide way for utilization of these compounds for CNS activity. It is also known that quinazolines possess CNS depressant activity. So, it is thought of worthwhile to condense isatins with 2-methylquinazolinone by making use of 3-keto group of isatin and 2-ethyl group of 2-methylquinazoline as shown in scheme-1 to get more potent compounds.

MATERIALS AND METHODS

Synthesis of isatins (Indole- 2, 3-diones) (III): The different isonitrosoacetanilides were prepared from the respective aromatic amines (I) viz. aniline, p-bromoaniline and p-toluidine etc. on reaction with chloralhydrate and hydroxylamine hydrochloride. Each of the isonitrosoacetanilide (II) was subjected to a dehydrative cyclization using sulphuric acid to yield the corresponding isatin (III)[7]. All these isatins thus prepared were identified by their physical constants reported in the literature[8]. Anthranilic acid (IV) has been converted to 2-methyl benzoxazinone (V) by refluxing with excess of acetic anhydride. This compound has been treated aniline and $POCl_3$ in presence of pyridine to get 2-methyl-3-phenyl-4-[3H] quinazolin-4-one (VI) [9].

Synthesis of 3-(3-phenyl quinazolin-4-one methylene-2-yl) indolin-2-ones (VII)

Each of the isatin (III) has been refluxed with 2-methyl-3-phenyl quinazoline-4-one in glacial acetic acid. The reaction mixture was poured on to crushed ice to get the light reddish crystalline solid relatively in good yields. However each of such compounds has been further purified by recrystallization from appropriate solvents. These compounds have been characterized as their respective 3-(3-phenyl quinazolin-4-one methylene-2-yl) indolin-2-ones (VII) by their physical, analytical, spectral data. For example the product obtained on condensation of isatin (III) with 2-methyl quinazolin-4-one (VI) in glacial acetic acid has yielded crystalline solid m.p. 260^0C. Its IR (KBr) showed absorption frequencies (in cm^{-1}) at 3057 (NH), 1703 (C=O), 1687 (C=O). The mass spectrum of the compound has shown its molecular ion peak (M^+) at m/z 368 and base peak at m/z 237.

Synthesis of 1-n- substituted amino methyl-3-(3-phenyl quinazolin-4-one-methylene-2-yl) indolin-2-ones (VIII)

An appropriate 3-(3-phenyl quinazolin-4-one methylene-2-yl) indolin-2-ones (VII) has been subjected to mannich reaction with three different secondary amines viz. dicyclohexylamine, piperidine and morpholine in presence of formaldehyde and alcohol. The products have been characterized as 1-N-substituted amino methyl-3-(3-phenyl quinazolin-4-one methylene-2-yl) indolin-2-ones

(VIII) based on their physical, analytical and spectral data. For example 3-(3-phenyl quinazolin-4-one methylene-2-yl) indolin-2-ones (VII) reacted with morpholine in presence of formaldehyde to get light yellowish solid, m.p. 228^{0}C. The IR (KBr) showed absorption frequencies (in cm^{-1}) at 1711 (C=O), 1685 (C=O). Mass spectrum of the compound showed molecular ion (M^+) peak at m/z 467 and base peak at m/z 237. The absence of characteristic peak for NH in IR spectra of compound (VIII), molecular ion peak of mass spectra of compound (VIII) at m/z 467 instead of molecular ion peak of compound (VII) at m/z 368 indicates the mannich reaction has been forwarded. The physical data of all the synthesized compounds are shown in Table-1 and Table-2.

Scheme-1

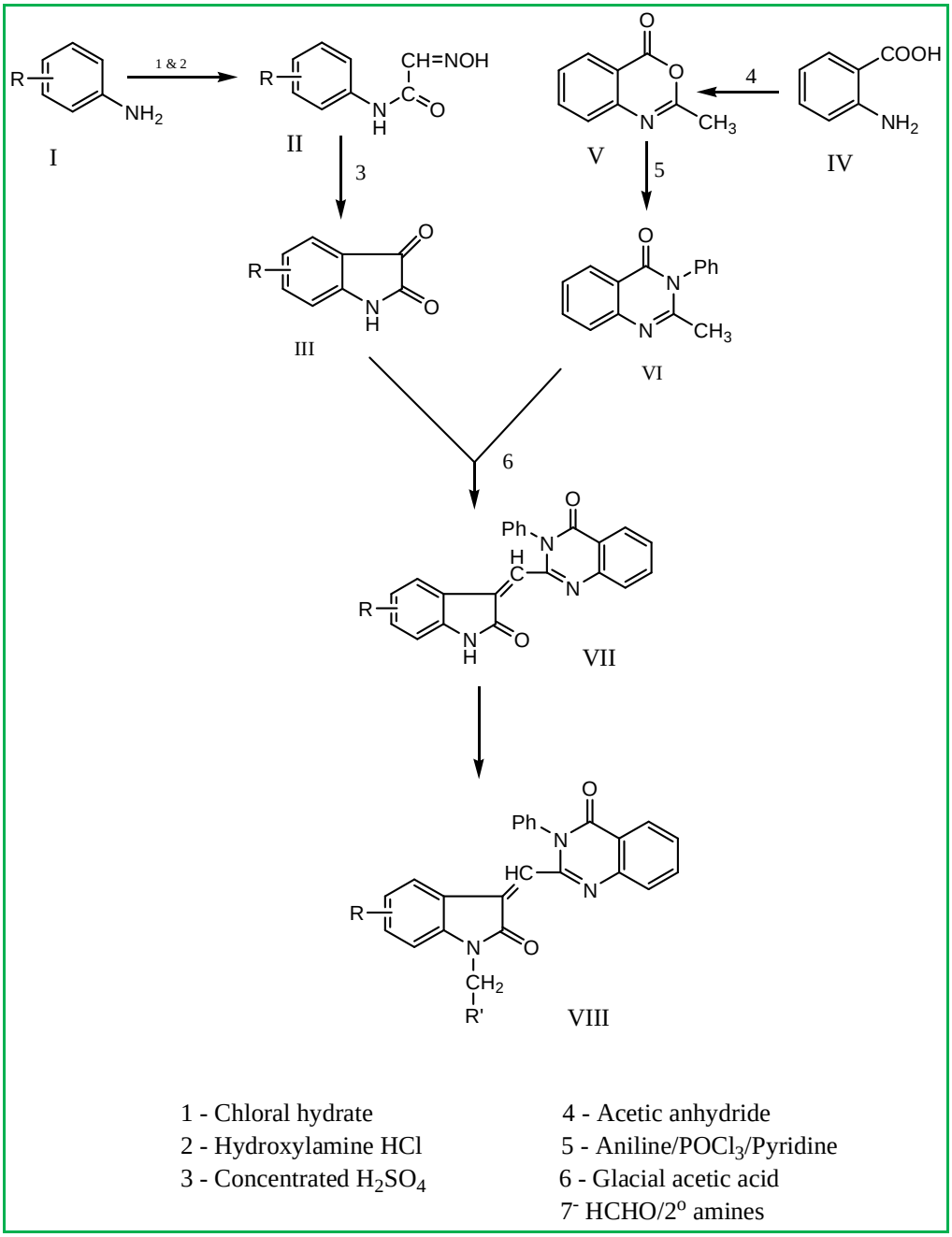
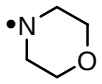
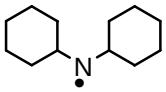
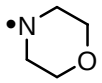
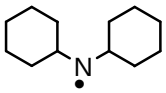
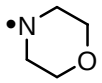


Table 1: Physical data of 3-(3-phenyl quinazolin-4-one methylene-2-yl) indolin-2-ones (VII)

S. No	Compound	R	m.p.(°C)	Yield (%)	Mol. Formula
1	VIIa	H	260	80	$C_{23}N_3O_2H_{15}$
2	VIIb	5-CH_3	245	85	$C_{24}N_3O_2H_{17}$
3	VIIc	7-CH_3	269	80	$C_{24}N_3O_2H_{17}$

Table 2: Physical data of 1-N- substituted amino methyl-3-(3-phenyl quinazolin-4-one-methylene-2-yl) indolin-2-ones (VIII).

S. No	Compound	R	R'	m.p.(°C)	Yield (%)	Mol. Formula
1	VIII a	H		228	90	$C_{28}N_4O_3H_{24}$
2	VIII b	H		220	85	$C_{29}N_4O_2H_{26}$
3	VIII c	H		190	92	$C_{36}N_4O_2H_{38}$
4	VIII d	5-CH_3		221	80	$C_{29}N_4O_3H_{26}$
5	VIII e	5-CH_3		200	75	$C_{30}N_4O_2H_{28}$
6	VIII f	5-CH_3		196	85	$C_{37}N_4O_2H_{40}$
7	VIII g	7-CH_3		226	76	$C_{29}N_4O_3H_{26}$
8	VIII h	7-CH_3		210	82	$C_{30}N_4O_2H_{28}$

Evaluation of 1-n- substituted amino methyl-3-(3-phenyl quinazolin-4-one-methylene-2-yl) indolin-2-ones (VIII)

It is known from the literature that indoles exhibited potentiating of pentobarbitone sleeping time, anticonvulsant, psychotropic and MAO inhibiting properties. Therefore, it has been felt worthwhile to screen the new 1-N-substituted amino methyl-3-(3-phenyl quinazolin-4-one methylene-2-yl) indolin-2-ones for CNS activity. For this purpose six new 1-N-substituted amino methyl-3-(3-phenyl quinazolin-4-one methylene-2-yl) indolin-2-ones (VIII) were synthesized. Six such compounds (VIIIa - VIIIe, VIIIg) have been synthesized starting from three isatins viz. isatin, 5-methylisatin and 7-methylisatin.

Action on Central Nervous System-Gross Behavioral Studies[10]

Healthy albino mice weighing between 20-25gms were used for this study. They were fasted for 24 hours and divided into groups of six animals each. Each of the test compound 10 mg was suspended in 0.3 ml of tween solution (one drop dissolved in 1ml of distilled water) and the volume made up with normal saline solution to get 10 mg/ml concentration. The suspension of test compounds was administered, intraperitoneally in a dose of 50 mg/kg (b.w). The control group animals received only the vehicle. The animals were observed for gross behavioral changes, continuously, for 7 hours starting from the administration of compounds. All the test compounds have produced depression in the test animals and no morality was observed. The gross behavioral changes are presented in Table-3. The locomotor activity was studied with Actophotometre before and after half an hour of administration of the test compounds. The results were calculated by paired 't' test and presented in Table-4.

Effect on Pentobarbitone – Induced Narcosis[11]

Healthy adult albino swiss mice weighing between 20 and 28 g. were fasted for 24hrs. Before the experiment and were divided into groups of six animals each. The test compounds were administered intraperitoneally at a dose of 50 mg/kg (b.w). The control group of animals was given the vehicle. After 30 min, pentobarbitone sodium was administered, intraperitoneally to all groups of animals at a dose of 35 mg/kg (b.w.). The time of administration of test compounds and pentobarbitone sodium, the time of loss and gain of righting reflex were recorded in all the groups of test animals and the effect on pentobarbitone sodium induced narcosis by the compounds were calculated by using the unpaired 't' test. The results are presented Table-5.

RESULTS, DISCUSSION AND CONCLUSION

Gross Behavioral Studies

The gross behavioral studies of the test compounds reveal that all the test compounds exhibited CNS depression in the mice. The other features observed were that of frequent excretion of urine.

Effect of Locomotor Activity

Table 4 pertaining to the results of the effect of the test compounds on locomotor activity of the mice shows that

all the test compounds have reduced the locomotor activity. Except VIII e increased locomotor activity which is found to be not significant. Compound VIII e (R=5-methyl, R^1 = piperdino) has exhibited more effect among all the compounds. Compounds VIII c and VII g were next to the compound VIII e in the order of reduction of locomotor activity.

Effect on Pentobarbitone Induced Sleep

The data on effect of the test compound on pentobarbitone induced narcosis is presented in Table 5. The results shown that all the test compounds have potentiated pentobarbitone sodium sleeping time from 87.00 to 136.33 min. The compound VIII d showed more activity with a potentiation of 136.33 min. Compound VIII c, VIII g and VIII e were found to be next in the order of potentiation of pentobarbitone sleeping time. Compounds with 5-methyl substitution on indole nucleus were found to be more active than the remaining compounds in their series.

Acknowledgements: The authors are very much thankful to the Principal, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, for providing necessary facilities during the work.

Table 3: Gross behavioral studies of 1-N- substituted amino methyl-3-(3-phenyl quinazolin-4-one-methylene-2-yl) indolin-2-ones (VIII).

Parameters observed	Time in Hours								
	1	2	3	4	5	6	7	24	48
I. Awareness								No Mortality	No Mortality
a. Alertness	---	---	---	---	+	+	+		
b. Visual Placing	---	---	---	---	---	---	---		
c. Stereo Type	---	---	---	---	---	---	---		
d. Passivity	+	+	+	+	---	---	---		
e. Writhing	---	---	---	---	---	---	---		
II. Mood									
a. Grooming	+	---	---	---	+	+	+		
b. Vocalization	---	---	---	---	---	---	---		
c. Restlessness	---	---	---	---	---	---	+		
d. Irritability	---	---	---	---	---	---	---		

All the test compounds were administered in a dose of 50mg/kg body weight (I.P.)

Table 4: Effect of 1-N-substituted amino methyl-3-(3-phenyl quinazolin-4-one-methylene-2-yl) indolin-2-ones (VIII) on Locomotor activity by paired't' test.

Compound	Before admin. Of drug(10 min.)		Before admin. Of drug(10 min.)		Significant levels**
	Mean	SD	Mean	SD	
VIII a	458.83	12.59	158.16	6.82	Sig.
VIII b	248.00	9.87	316.33	7.12	NS
VIII c	526.66	4.88	212.66	6.02	Sig.
VIII d	422.83	4.16	158.33	8.70	Sig.
VIII e	528.67	6.12	150.33	3.77	Sig.
VIII g	528.66	8.01	228.83	11.02	Sig.

** P < 0.001, n = 6, Sig = Significant, NS = Not significant

All the test compounds were administered in a dose of 50 mg/kg body weight (I.P.)

Table 5: Effect of 1-N- substituted amino methyl-3-(3-phenyl quinazolin-4-one-methylene-2-yl) indolin-2-ones (VIII) on pentobarbitone induced sleeping time by unpaired't' test.

Compound	Control (Time in minutes.)		Test (Time in minutes.)		Significant levels**
	Mean	SD	Mean	SD	
VIII a	31.83	5.42	56.66	26.76	NS
VIII b	31.83	5.42	---	---	NS
VIII c	31.83	5.42	102.83	12.48	Sig.
VIII d	31.83	5.42	136.33	36.58	Sig.
VIII e	31.83	5.42	87.00	37.32	Sig.
VIII g	31.83	5.42	94.66	20.74	Sig.

** P < 0.001, n = 6, Sig = Significant, NS = Not significant;

All the test compounds were administered in a dose of 50 mg/kg body weight (I.P.)

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