Pakistan Journal of Pharmaceutical Sciences
Vol. 16, No.1, January 2003, pp.73-77

SYNTHESIS OF SOME PHENACYL DERIVATIVES OF 1-METHYL-7-METHOXY-β-CARBOLINE AND THEIR BEHAVIOURAL STUDY

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ABSTRACT:

In the present study two phenacyl derivatives of Harmaline; 2-(7-Methoxy-1-methyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-1-(3-nitro-phenyl)-ethanone and 1-(3,4-Dihydroxy-phenyl)-2-(7-methoxy-1-methyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-ethanone were synthesized and evaluated for their effect on behaviour of mice, only meta-nitro phenacyl derivative showed activity, which can be compared with parent compound.

INTRODUCTION

Harmaline (1-methyl-7-methoxy-β-carboline) have been received enormous attention because of invaluable therapeutic activities. Carboline and its related compounds have been isolated from plants like *Banisteria caapi*, *Peganum hermala*, *Prestonia amazonicum* and number of other plants. Recently different new alkaloids were reported in literature having beta carboline ring system (Harwood *et al.,* 2003 and Samoun *et al.,* 2002) and different other carboline alkaloids found in food were studied for their antioxidant activity (Herraiz *et al.,* 2002). Different kinds of derivatives having carboline ring system have also been synthesized and they exhibited pronounced pharmacological and biological effects (Maw *et al.,* 2003 and Park *et al.,* 2003). Carboline containing moieties were found effective on CNS (Kitajima *et al.,* 2002, Fuentes *et al.,* 1971, Tonks, 2003, Boksa *et al.,* 2001, Pokk & Vali, 2001, Krazem *et al.,* 2001 and Suaudeau *et al.,* 2000), smooth muscles (Shi *et al.,* 2001), cardiovascular system (Aarons *et al.,* 1977, Shi *et al.,* 2001, Khawaja *et al.,* 1978 and Riba *et al.,* 2003) and vision (Rojas *et al.,* 1971) as well as platelet binding activity was also evaluated (Given & Longenecker, 1983). Work has also been done on toxicity profile (Lamchouri *et al.,* 2002), antitumour activity (Fontona *et al.,* 2002 and Ishida *et al.,* 1999) of different carboline analogues and the ability of different microbes to transform the carboline containing alkaloids (Herath *et al.,* 2003). The potentials of carboline ring system as significant therapeutic agent led to study different synthesized derivatives for their biological activity.

EXPERIMENTAL

Synthesis

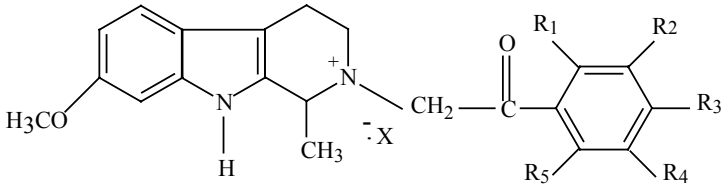
Reagents, Chemicals and Instruments:

Reagents were purchased from Aldrich Chemical Company. All solvents are reagents grade. Reactions were monitored by TLC using silica gel type 60 P_{254} of E. Merk for preparing TLC

plates and visualized with iodine vapours. All melting points were recorded on Gallenkamp melting point apparatus and are uncorrected. Solid calcium sulphate from E. Merk was used for drying reaction product after workup. Ultraviolet (UV) spectra were recorded in methanol on a Hitachi U-3200 spectrophotometer. Infra Red (IR) spectra were measured on a Shimadzu IR 460 spectrophotometer using KBR disc. Mass Spectra (MS) were determined on Varian Massen spektrometer MAT 311A spectrometer. Nuclear Magnetic Resonance (NMR) spectra were recorded in DMSO-d_6 on Bruker AM-300 and 400 spectrometer operating at 300 and 400 MHz.

General Method

Equimolar quantities of 1-methyl-7-methoxy-β-carboline and substituted phenacyl halides were dissolved in acetone (75ml) separately. They were mixed and stirred for 4-6 hours at room temperature. The reaction mixtures were refluxed for 48-72 hours and kept in dark for 3-5 days. Reactions were continuously monitored with TLC. The products were recrystallized from appropriate solvents to give the purified products.



(I) R_1 = H R_2 = NO_2 R_3 = H R_4 = H R_5 = H X = Br
(II) R_1 = H R_2 = OH R_3 = OH R_4 = H R_5 = H X = Cl

Characterization of Compounds:

2-(7-Methoxy-1-methyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-1-(3-nitro-phenyl)-ethanone (I)

State: Orange needle shaped crystals
***Melting Point*:** 230 ± 2°C
Yield: 71%

UV λ_{max} (MeOH) nm; 372, 262. IRυ_{max} (KBr) cm^{-1}: 460, 3120,1720, 1630, 1580, 1550, 1218. ^{1}HNMR (d_6-DMSO, 400MHz): δ 2.48 (m, 1H, *H*-1), 2.63 (s, 2H, C*H*2), 3.1 (t, 2H, *J*= 8.61, *H*-3, *H*-3'), 3.2 (m, 2H, *H*-4, *H*-4'), 3.84 (s, 3H, C*H*3) 4.5 (d, 3H, *J*=7.0, C*H*3), 6.81 (dd, 2H, *J*=8.90, *J*=2.11, *H*-6, *H*-5') 6.87 (dd, 2H, *J*= 7.97, *J*=2.2, *H*-8, H-6'), 6.85 (dd, 2H, *J*=8.90, *J*=2.0, *H*-2', *H*-4') 7.65 (d, 1H, *J*=8.8, *H*-5), 12.18 (s, 1H, *H*-9)

1-(3,4-Dihydroxy-phenyl)-2-(7-methoxy-1-methyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-ethanone (II)

State: Grey crystalline powder
***Melting Point*:** 242 ± 2°C
Yield: 65%

UV λ_{max} (MeOH) nm; 386, 252; IRυ_{max} (KBr) cm^{-1}:3475, 3180, 1710, 1630, 1300, 1230. ^{1}HNMR (d_6-DMSO, 400MHz):δ 2.48 (d, 3H, *J*=7.2, C*H*3), 2.4 (m, 2H, *H*-4, *H*-4'), 2.49-2.50 (m, 1H, *H*-1), 3.2(t, 2H, *J*=9.10, *H*-3, *H*-3'), 3.40 (s, 2H, C*H*2), 3.84 (s, 3H, C*H*3), 6.83 (dd, 2H, *J*=6.84, *J*= 2.15, *H*-6, *H*-5'), 6.80 (dd, 2H, *J*=8.9 *J*=2.11, *H*-8, *H*-6'), 6.91 (dd, 1H, *J*= 19.92, *J*=2.22, *H*-2') 7.69 (d, 1H, *J*=8.9, *H*-5), 11.83 (s, 2H, O*H*), 12.69 (s, 1H, H-9).

Effect on CNS:

Animals:

Female albino mice +NMRI strain weighing 25-30 mg.

Drugs and Chemicals:

Harmaline (Merk), Test compounds, Water for injection, DMSO of Merk

Method:

For experiment, animals were divided into four groups, (n=6), among which one group served as control. (water for injection/2% DMSO). Test compounds were administered *i.p.* at the dose of 50mg/kg. The effect of parent compound and synthetic derivatives on behaviour was observed.

RESULT AND DISCUSSION

Effect of the parent and synthetic compounds is given in the Table.

Table

Showing the effect of 1-methyl-7-methoxy-β-carboline and its Phenacyl derivatives on mice behaviour

	Control	Harmaline (1-methyl-7-methoxy-β-carboline)	2-(7-Methoxy-1-methyl-1,3,4,9-tetrahydro-b-carbolin-2-yl)-1-(3-nitro-phenyl)-ethanone (I)	1-(3,4-Dihydroxy-phenyl)-2-(7-methoxy-1-methyl-1,3,4,9-tetrahydro-b-carbolin-2-yl)-ethanone (II)
Dose (mg/kg)	–	50	50	50
Route of administration	i.p.	i.p.	i.p.	i.p.
Time of onset (minutes)	–	10	10	–
Time of duration (minutes)	–	120	130	–
Tremor	_	++++	+++	_
CNS stimulation	_	+++	+++	_
Aggressive behaviour	–	+++	+++	–
Increased motility	_	++	+++	_

During investigation mice treated with parent compound (1-methyl-7-methoxy-β-carboline) possessed extreme hyperactivity and on touch became aggressive, the motility of animal increased. Harmaline is a powerful stimulating agent and causes excitation of central nervous system. Compound induced tremor (generalized convulsions) within 10 minutes, which persisted for two hours.

2-(7-Methoxy-1-methyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-1-(3-nitro-phenyl)-ethanone (I) produced severe tremors within ten minutes, which lasted for more than two hours. They showed CNS excitation and possessed hyperactivity with loss of conditioned response. Motility of animals increased and they showed aggressive response on touch.

In the case of *1-(3,4-Dihydroxy-phenyl)-2-(7-methoxy-1-methyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-ethanone (II)* no effect was observed though the compound was found inactive apparently but the compound can be studied further for CNS effect by neurochemical estimation.

Comparing the activity of synthesized derivatives with parent compound only compound (I) exhibited significant effect and showed more or less the same response as observed by parent compound with same time of onset and duration of action. This result showed that by adding phenacyl halide having meta nitro group did not change the activity and retain the effect of parent compound. Significant activity of compound (I) and no effect by compound (II) is also very interesting because SAR of two compounds revealed that by removing NO_2 group of phenyl ring of phenacyl moiety and incorporating OH group in the same phenyl ring make the compound inactive. These results may suggest that substitution in the phenyl ring is responsible for significant effect in compound (I) and no response for compound (II).

The present study is only the preliminary screening and results are encouraging enough and will provide a better understanding for exploration of different biological fronts to get a compound with profound therapeutic activity.

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