Analgesic activity of alkyl piperidine derivatives

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Abstract: Piperidine is the most significant scaffold which reveals therapeutic potential because of its conformationally flexible nature. During the course of present investigations synthetic quaternary salts of alkyl piperidine with various phenacyl bromides were explored for their possible analgesic activity. Compounds I analogs (1a-1f) and compound II analogs (IIa-IIf) showed varying degree of analgesic activity when compared with pethidine as standard and its duration by tail immersion method.

Keywords: Alkyl piperidine derivatives, analgesic activity, SAR.

INTRODUCTION

Pain can devastate human quality of life has been widely accepted and considered to be a main challenge in medicine (Giovannoni *et al.,* 2007, Nkomo *et al.,* 2010). This is unpleasant sensation which results from a risky sensorial stimulation and attentive the body about current damage to its organs and tissues (Ruoff *et al.,* 2003, Siddiqui *et al.,* 2010). For the treatment of pain two major classes of traditional analgesics include nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids (Cesari *et al.,* 2006, Sakhteman *et al.,* 2011).

Piperidines and their derivatives played a key role as pharmacophore in the pharmaceutically active molecules, naturally occurring alkaloids, pharmaceuticals, agrochemicals and as synthetic intermediates with interesting biological, physical and pharmacological properties (Watson *et al.,* 2000, Rubiraltan *et al.,* 1991, Aejaz *et al.,* 2012, Khan *et al.,* 2006, Khan *et al.,* 2005, Saify *et al.,* 1999, Saifiy *et al.,* 2000, Khalid *et al.,* 2012). Add our references Therefore a huge amount of efforts have been devoted to their construction by synthetic chemists all over the world (Weintraub *et al.,* 2003). Therapeutically active agents containing piperidine ring as essential part are well known for their analgesic, antiinflammatory, antidepressant, antipsychotic, antiviral, antimicrobial, agonistic, and antagonistic activities (Janssens *et al.,* 1986). New opiates or narcotic analgesic were discovered leading to molecular modifications of these compounds (Ahmadi *et al.,* 2005).

It had been reported that some new derivatives of phencyclidine (1-(1-phenylcyclohexyl) piperidine have biological importance, by introduction of a hydroxyl group at position 2 of the cyclohexane ring was proved to be more hydrophilic (Saify *et al.,* 2005, Mushtaq *et al.,* 2005). During the course of last few years attempts have been made to synthesize a simple molecule having all the structural similarity to that of morphine or pethidine (Ippei Sato *et al.,* 2008) without opioids properties.

In view of above-mentioned reports, in current study synthesis and analgesic potential of alkyl piperidines analogs (1a-1f) and compound II analogs (IIa-IIf) was carried out. From this study it was found that these alkyl piperidines showed significant potential with longer duration of analgesic action. The characterization of these synthesized derivatives data has been published (Sarwat *et al.,* 2013) by different spectroscopic techniques such as U.V /Visible, I.R, Mass and ^{1}H NMR respectively.

MATERIALS AND METHODS

Chemistry

piperidine-2-methanol and Piperidine-2-ethanol (0.01 mol) and various phenacyl bromide (0.01mol) were dissolved separately in ethanol (20mL) and then mixed together in a round-bottom flask added K_2CO_3 (Scheme-1). Reflux reaction mixtures. The reaction completion was monitored by periodic TLC. The mixture was stirred at reflux for 3h. Cool the mixture to rt and partitioned between brine and EtOAc, dried the organic layer over MgSO4, filtered, and concentrated in vacuo, recrystallized from MeCN to yield the pure product (Distasi *et al.,* 1988).

Determination of analgesic activity

Material and Method

This activity was carried out on white Albino mice of either sex (locally breed) weighing between 20-30gm, purchased from Agha Khan Medical University and Hospital, Karachi. The compounds were tested for their analgesic activity as antinociceptive effect against thermal stimuli (tail flick method). Groups of ten animals were

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maintained under standard 12h light/12h' dark temperature 25±1°C, fed with frequently accessed diet and water.

Compounds were dissolved in 30% DMSO and injected to the test animals intraperitoneally at the doses of 50 mg/kg body weight. Pethidine (50mg/kg) was used as a standard drug while the control group receiving 30% DMSO always ran parallel to the compound treated groups through modified method (Janssen *et al*., 1963). Mice were manipulated in such a position that one-third of the tail (already marked) was immersed in water bath, thermostatically maintained at 51°C. The withdrawal time of the tail from hot water (in seconds) was noted as the reaction time or tail flick latency. The initial readings were taken immediately before administration of test and standard drugs and then 30, 60, 90, 120, 150 and 180 minutes after the administration of compounds. The criteria of analgesia was the difference in post drug and pre drug latency which was greater than two times the pre drug average latency (Alcaraz *et al*., 1989). Mean increase in latency after drug administration or analgesia was calculated. Analgesia TFLD was calculated as follows:

Analgesia TFLD=Post drug tail flick-Pre drug tail flick latency

STATISTICAL ANALYSIS

Analgesic activity was expressed as TFLD±SEM in terms of seconds. Student's t-test was performed for Statistical analysis and in which the values were considered either considerable or highly considerable when $P<0.05$ or $P<0.01$ respectively. All statistical procedures were fulfilled according to the method in (Alcaraz *et al*., 1989).

RESULTS

The results of newly synthesized alkyl piperidine derivatives are shown in graphs (fig.1, 1a-1f; 2, 2a-f).

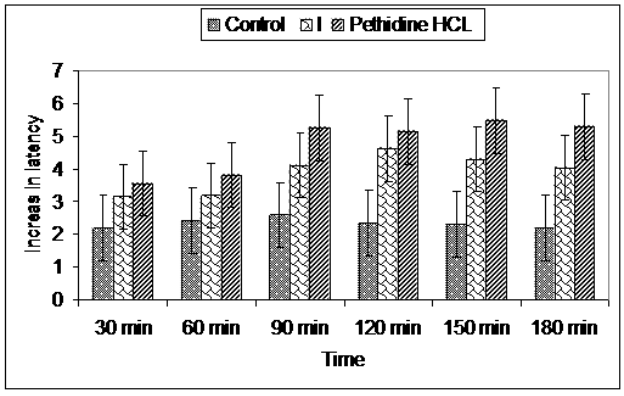

Fig. 1: Analgesic activity of Piperidine-2-methanol I by tail immersion method

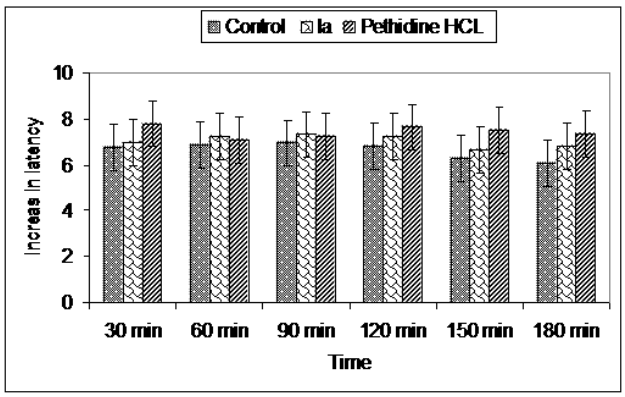

Fig. 1a: Analgesic activity of 2-hydroxymethyl-1-[(3-nitro-phenyl)-2-oxoethyl]-piperidinium bromide 1a by tail immersion method

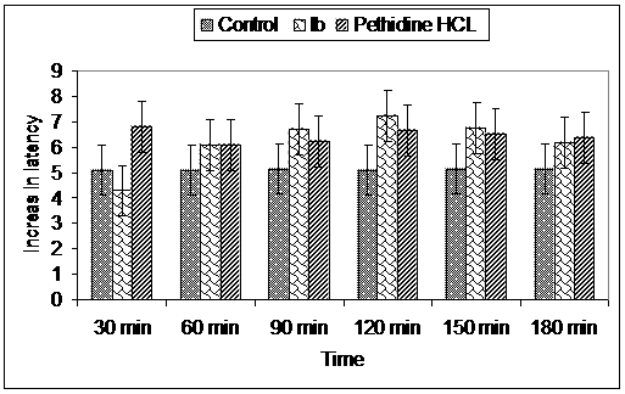

Fig. 1b: Analgesic activity of 2-hydroxymethyl-1-[(4-bromo-phenyl)-2-oxoethyl]-piperidinium bromide 1b by tail immersion method

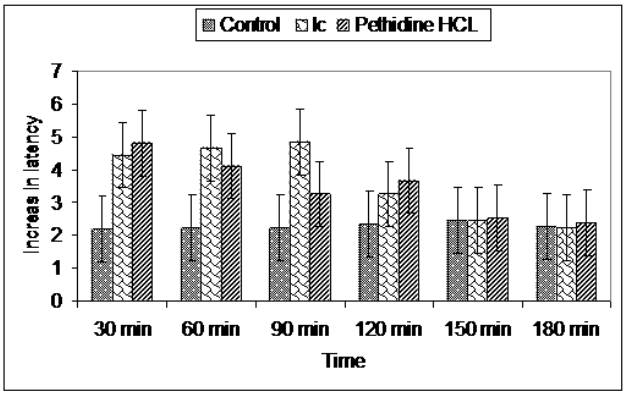

Fig. 1c: Analgesic activity of 2-hydroxymethyl-1-[(4-fluoro-phenyl)-2-oxoethyl]-piperidinium bromide 1c by tail immersion method

DISCUSSION

Biological activity

The alkyl piperidine-2-methanol I, and piperidine-2-ethanol II were taken as a starting material and synthesized their substituted derivatives and screened for antinociceptive activity. These compounds showed

varying degree of antinociceptive properties. These compounds show varying degrees of analgesia, its duration by tail immersion method (A Ahmadi *et al.*, 2005). Analgesia produced by the test compounds is represented as mean increase in latency after drug administration (TFLD ± SEM) in seconds. All the six analogs 1a-1f from piperidine-2-methanol and seven analogs from piperidine-2-ethanol IIa-IIf have showed varying degree of analgesic activity. The results are show in tables 1-2f and corresponding fig. (1 to 2f), it is evident from the results obtained that both the parent compounds already possessed a low degree of analgesic activity throughout the whole experiment. Piperidine-2-metnanol I showed its onset of action at 30min (fig. 1) and piperidine-2-ethanol II at 90min (fig. 2), after the administration through intra peritoneal route which persisted 180min. Compound I remained active for 120 min and the activity of compound II also persisted for150 min, as compared to the standard drug. The onset of action was late and duration was short. The results were non-significant throughout the experiment.

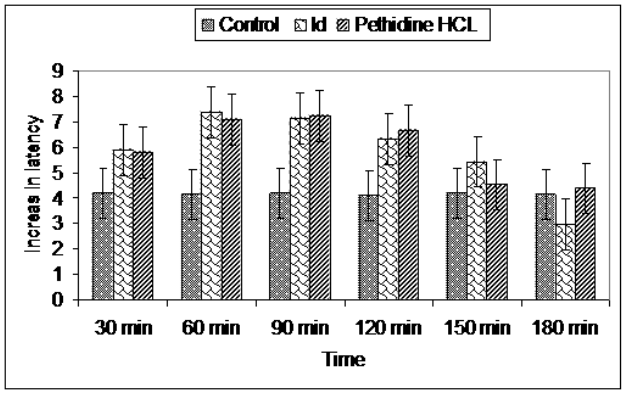

Fig. 1d: Analgesic activity of 2-hydroxymethyl-1-[(4-nitro-phenyl)-2-oxoethyl]-piperidinium bromide 1d by tail immersion method

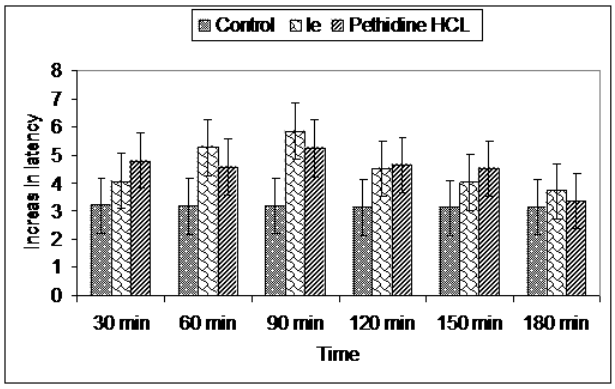

Fig. 1e: Analgesic activity of 2-hydroxymethyl-1-[(4-methoxy-phenyl)-2-oxoethyl]-piperidinium bromide 1e by tail immersion method

Comparing the analgesic effects of their derivatives, it was found that some of the derivatives posses more analgesic activity. In case of compound 1a, the onset of action (fig. 1a) was fast and highly active as compared to control and less active as compared to standard drug and persisted for 150min and fall down gradually up to 180 min but not significantly as compared to standard drug. However, the activity is significant as compared to the control. The onset of action is early and duration is longer lasting.

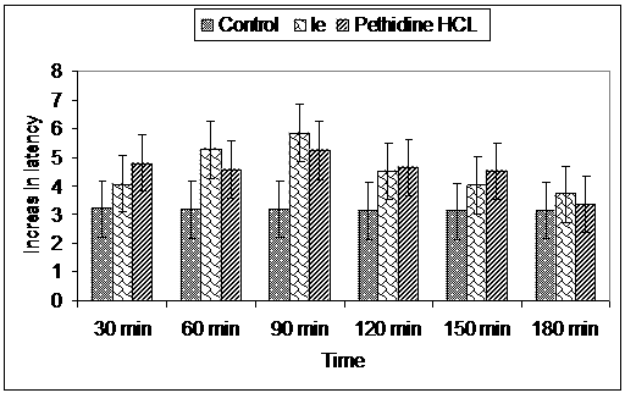

Fig. 1f: Analgesic activity of 2-hydroxymethyl-1-[(4-chloro-phenyl)-2-oxoethyl]-piperidinium bromide 1f by tail immersion method

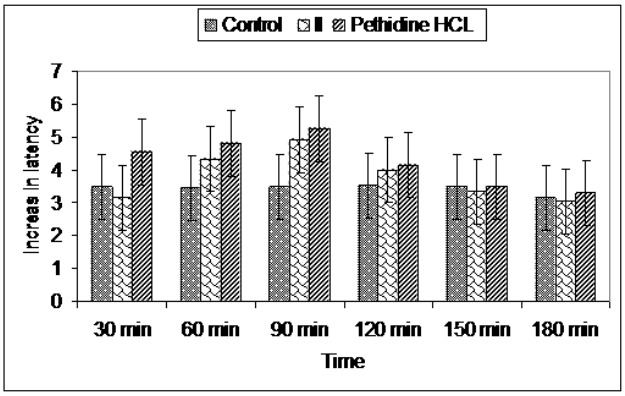

Fig. 2: Analgesic activity of Piperidine-2-ethanol II by tail immersion method.

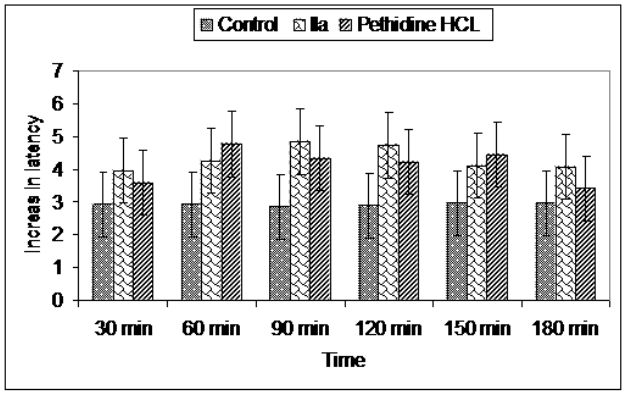

Fig. 2a: Analgesic activity of 2-hydroxy ethyl 1-(4-bromo-phenyl)-2-oxoethyl piperidinium bromide 2a by tail immersion method

Compound 1b (fig. 1b) showed its onset of action at 60 minutes and persisted for 150min and falls down

gradually up to 180min and remains significant as compared to control. As compared to standard drug the activity is significant and longer lasting for 150min and decreases at 180 min.

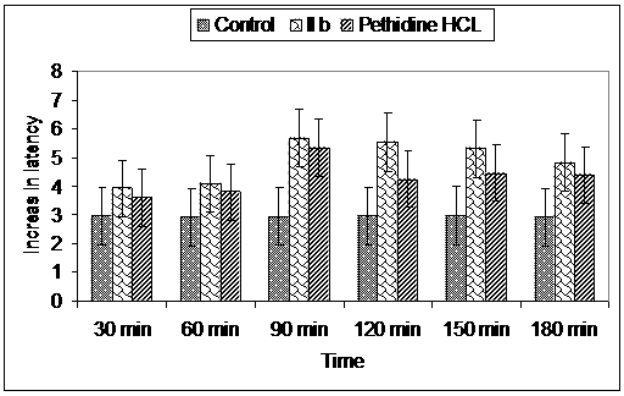

Fig. 2b: Analgesic activity of 2-hydroxy-ethyl-1-[(4-fluoro phenyl)-2-oxoethyl]-piperidinium bromide 2b by tail immersion method

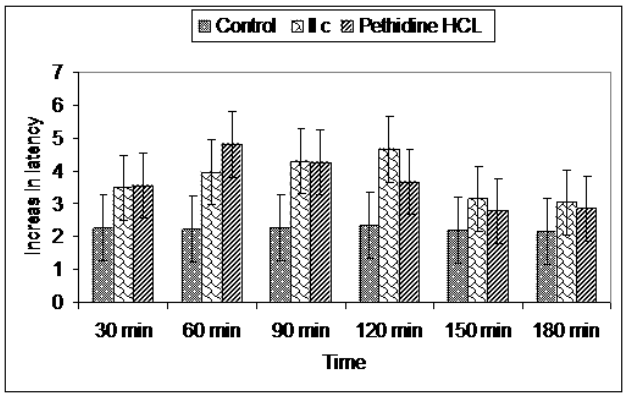

Fig. 2c: Analgesic activity of 2-hydroxy-ethyl-1-[(3-nitro phenyl)-2-oxoethyl]-piperidinium bromide 2c by tail immersion method

Compound 1c (fig. 1c) showed its onset of action at 30 minutes and persisted for150min and fall down gradually up to 180min and remain significant as compared to control. The activity is significant at 90min as compared to the standard drug. The onset of action is early and the duration is short.

Compound 1d (fig. 1d) showed its onset of action at 30 minutes and persisted for 150 minutes but remain significant as compared to control and the standard drug. Compound 1e (fig. 1e) showed its onset of action at 30 min the effect was increasing for 90 min then fall down gradually up to 180 min. Highly significant analgesia was observed at 60 to 90min and potency was more as compared to the standard drug. The effects were significant and more potent up to 180min. as compared to the standard drug. Compound 1f (fig. 1f) showed its onset of action at 60min. and persist for 90min and little bit decrease at 120 and 150min but the activity was highly significant at 60, 90 and 180min as compared to control and the standard drug.

Compound 2a (fig. 2a) showed its onset of action at 30 min persisted for 120 min and gradually fall down at 150 min. The activity was significant at 30, 90, 120 and 180 min as compared to control and the standard drug.

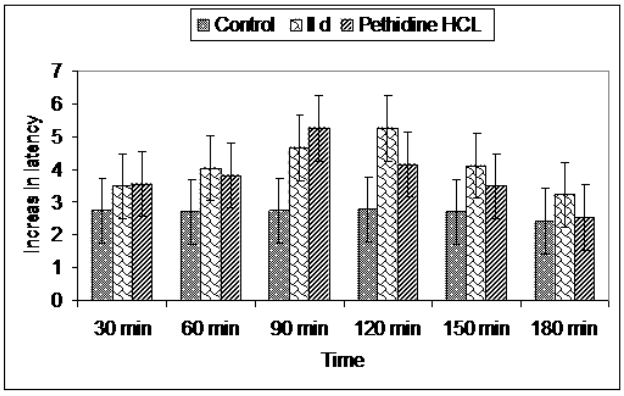

Fig. 2d: Analgesic activity of 2-hydroxy ethyl 1-(4-nitro-phenyl)-2-oxoethyl piperidinium bromide 2d by tail immersion method

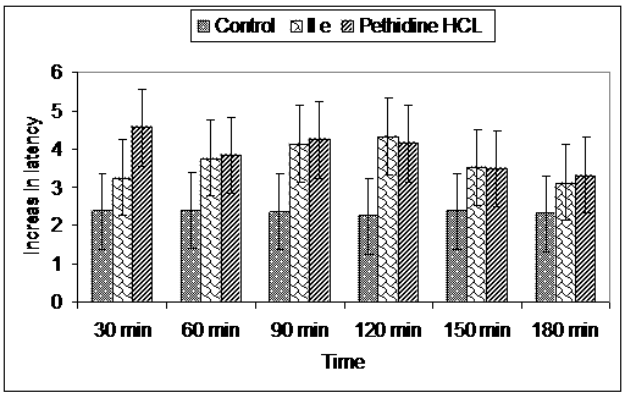

Fig. 2e: Analgesic activity of 2-hydroxy ethyl 1-(2-nitro-phenyl)-2-oxoethyl piperidinium bromide 2e by tail immersion method

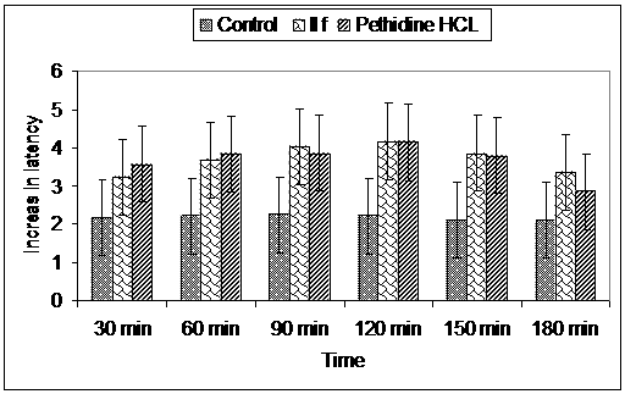

Fig. 2f: Analgesic activity of 2-hydroxy-ethyl-1-[(3', 5', dinitro-phenyl)-2-oxoethyl]-piperidinium bromide 2f by tail immersion method.

Compound 2b (fig. 2b) showed its onset of action at 30 min and sustained for 180min but the activity was significant and potent as compared to control and the standard drug throughout the experiment. Compound 2c

(fig. 2c) showed its onset of action at 30minutes and continued for 180min. and fall down at 60min. Maximum effects were attained in 2hrs and then decreased. The activity was significant as compared to control and more potent than that of the standard drug.

Compound 2d (fig. 2d) showed its onset of action at 30 min. increased gradually up to 120min at which highly potent analgesia was observed. Then there was a gradual decrease in analgesic effect up to 180min but the activity was significant as compared to control and more potent than that of the standard drug. Compound 2e (fig. 2e) showed its onset of action at 30min and persisted for 180 min and fall down gradually at 150 and 180min but the activity was significant from 60 to 180min and were comparable to the standard drug. The compound had shown longer lasting effects.

Compound 2f (fig. 2f) showed its onset of action at 30 min. and persisted up to 180min. The effects were highly significant up to 180min. as compared to control. The results were also comparable to the standard drug and interestingly similar to that of the previous compound 2e.

Comparing the halogenated derivatives as bromine, chlorine and fluorine, it was found that the analgesic effects were mildly changed and the presence of different halogens resulted in different levels of analgesia while somewhere the analgesic effects were comparable such as in the case of chloro and bromo derivatives. It was also interesting to note that the derivatives displaying significant analgesic effects had one thing common that is the substitution at *para* position of phenyl ring.

It was also observed that almost all the derivatives exhibited significant analgesic effects after one hour while some of the compounds produced highly significant analgesia after 30 min of administration such as compounds 2 (table 2, fig. 2) and 2b (table 2b, fig. 2b). Compound 2b showed significant analgesic effect after 90min of administration as compared to 6 (table 6, fig. 6), which started showing analgesic action after 30 min but the effect sustained till 3h in all three compounds. The fluoro derivative 1c (table 1c, fig. 1c) showed its onset of action after 30min of administration and remained highly significant till 90min. After 90min. the analgesic effect had decreased.

Table 1e and fig. 1e showed the methoxy derivative of alkyl piper dine that expressed highly significant effects after 30 min. and continued till 180 min. Compound 1b (table 1b, fig. 1b) showed analgesia after 1h and remained active up to 2.5h. The onset of action in the compound Id (table 1d, fig. 1d) was appeared in 30 minutes and the effect was significant up to three hours. The compound If (table 1f, fig. 1f) showed highly significant analgesic effects after 60min. of administration and the effect was persisted till 180min.

Maximum response of compound 2a (table 2a, fig. 2a) was observed at 30 min. and remained significant up to 3 h. Compound 2b (table 2b, fig. 2b) showed its onset of action at 30 min and sustained up to 180min. but the activity was significant as compared to control and the standard drug throughout the experiment.

Among the nitro derivatives, compounds 2c, 2d and 2e showed analgesic effect throughout the experiment with highly significant effects at 90 and 120min and little bit decreased at 150 and 180min but did not vanished. Whereas compound 2d and 2f both showed pronounced activity from 30 to 180min. Both compounds also exhibited more potency as compared to the standard drug (pethidine). Therefore, among the nitro derivatives, compound with $-NO_2$ group at *para* position showed highly significant effect as compared to *meta* and *ortho* analogs but the same group was also responsible for longer duration of action.

From the above-mentioned discussion on analgesic effects of all of these synthesized derivatives (I-IIf), it can be predicted that the possible mechanism of action was related to their narcotic analgesic effects. Moreover, comparing all the compounds broadly on the basis of different functional groups attached to the benzyl ring, it can be suggested that the phenyl moiety was responsible for the pronounced analgesic activity of the compounds.

CONCLUSION

The alkyl piperidine derivatives I-IIf were found generally more potent analgesics as compared to the parent compounds. Comparing all the compounds on the basis of different functional groups attached to the benzyl ring, compounds with phenyl substitution at *para* position showed better analgesic effects.

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