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SHORT COMMUNICATION

Synthesis and pharmacological evaluation of novel *cis* and *trans* 3-substituted anilidopiperidines

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Abstract

Background 4-Anilidopiperidine class of synthetic opioid analgesics, with it's representative fentanyl, are by far the most potent and clinically significant for the treatment of the severe chronic and surgical pain. However, side effects of μ-opioids are often quite serious. In order to improve the pharmacological profile of this class of opioid analgesics, a novel fentanyl analogs were designed, synthesized and evaluated in vivo for their antinociceptive activity.

Methods The title compounds were prepared using known synthetic transformations, including *N*-bromoacetamide mediated Hofmann rearrangement, highly selective carbamate cleavage with trimethylsilyl iodide and dehydration of carboxamide group to nitrile in the presence of $SOCl_2$. The antinociceptive activity of the synthesized compounds was determined by tail-immersion and formalin test.

Results The scalable synthetic route towards novel fentanyl analogs bearing nitrogen groups in position C_3 of piperidine ring is designed. In addition, Hofmann rearrangement was substantially improved for the more efficient synthesis of previously published 3-substituted fentanyl analogs. The series of ten fentanyl analogs was tested in vivo for their antinociceptive activity. The most potent compound of the series was found to be *cis*-**4**, based on the determined ED_{50} values in tail-immersion test.

Conclusion Of ten compounds tested for their antinociceptive activity, compound *cis*-**4** is characterized by high potency, rapid beginning and short duration of action and due to this might be incorporated in different pharmaceutical forms.

Keywords Opioid · Fentanyl · Antinociceptive · Anilidopiperidine

Introduction

Pain management is one of the major fields of medicine and important goal in public health. While the inflammation-related pain is usually treated by COX inhibitors (e.g. aspirin, ibuprofen, paracetamol), severe chronic and surgical pain is mainly managed by opioid analgesics. Of these, μ-opioid agonists are by far the most potent and clinically significant. Selective κ and δ agonists are much less effective [1]. In addition to pain treatment, opioids are also useful in the conditions such as acute pulmonary edema, cough, diarrhea and shivering [2]. However, side effects of μ-opioids are often quite severe, including acute life-threatening respiratory depression, sedation, constipation, nausea, as well as chronic tolerance and physical dependence. Due to the extensive opioid misuse or abuse, opioid addiction is serious, worldwide health issue [3]. Among several classes of important opioid drugs, fentanyl is a prototype of the 4-anilidopiperidine class of synthetic opioid analgesics [4]. Fentanyl is 80–100 times more potent than morphine, having fast onset and a relatively short duration of analgesia [5, 6]. Fentanyl congeners in clinical use (alfentanil, sufentanil and remifentanil) are also very potent, short-acting drugs. Fentanyl transdermal patches effectively manage some types of chronic pain, principally terminal cancer pain [7]. Numerous

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fentanyl analogues have been synthesized in the past several decades, both to establish the structure–activity-relationship (SAR) and to find drugs with superior pharmacological profile (potency, selectivity, pharmacokinetics). Two such drugs, carfentanil and thiafentanil become useful veterinary opioids [5, 8, 9].

This study aims at improving our previously published synthetic procedure [10, 11] and to examine the antinociceptive activity of some new fentanyl analogues. The tests involved models of phasic (tail-immersion) and tonic (formalin test) pain in rats. Relationship between the structure of new compounds and the experimentally determined antinociceptive activity (potency and the duration of action) is briefly discussed.

Material and methods

General procedure for the synthesis of compounds 2 and 4

To a magnetically stirred solution of carboxamide (0.9 mmol, 1.0 equiv.) in MeOH (3 mL), $LiOH{\cdot}H_2O$ (14.0 equiv) and NBA (4.0 equiv.) were added. Mixture was allowed to steer at 60 °C, in dark. Reaction was monitored by TLC, on SiO_2 plates, using mixture of *n*-hexane/EtOAc = 1:1 and CH_2Cl_2/MeOH = 9:1, as eluent. After 5 min, mixture was concentrated by rotary evaporator to give a residue which was mixed with 1 M solution of NaOH. The mixture was extracted with 2 × 25 mL of CH_2Cl_2. Organic layers were combined and concentrated by rotary evaporator. Obtained crude product was purified by dry flash chromatography.

Procedure for the synthesis of compounds 5

To a magnetically stirred solution of carboxamide **3** (0.2 mmol, 1.0 equiv.) in DMF (2 mL), $SOCl_2$ (2.0 equiv) was added. Mixture was allowed to steer at 25 °C. Reaction was monitored by TLC, on SiO_2 plates, using mixture of *n*-hexane/EtOAc = 6:4, as eluent. After 3 h, mixture was concentrated by rotary evaporator to give a residue which was dissolved in CH_2Cl_2 and washed with brine (2 × 20 mL). Organic layer was separated, and concentrated by rotary evaporator. Obtained crude product was purified by dry flash chromatography (SiO_2; *n*-hexane/EtOAc = 8:2–2:8).

Procedure for the synthesis of compounds 6

To a magnetically stirred solution of carbamate **4** (0.24 mmol, 1.0 equiv.) in dichloroethane (2 mL), TMSI (3.5 equiv.) was added. Mixture was allowed to steer at 25 °C, in dark. Reaction was monitored by TLC, on SiO_2 plates, using mixture of CH_2Cl_2/MeOH = 9:1, as eluent. After 48 h, excess of MeOH was added and the mixture was concentrated by rotary evaporator. 1 M Solution of HCl was added to residue, and extracted with 3 × 15 mL CH_2Cl_2. 1.5 M K_2CO_3 was added to aqueous layer (pH ~ 11), and extracted with 3 × 15 mL of CH_2Cl_2. Organic layers were combined and concentrated by rotary evaporator affording the crude product. There was no need for additional purification of the product.

In vivo determination of antinociceptive activity

The antinociceptive activity was determined by the tail-immersion [5] and the formalin test [12]. The experiments were approved by the Local Ethical Committee of the Faculty of Medicine, University of Belgrade (permit No. 5784/1) and the Ethical Council of the Ministry of Agriculture, Forestry and Water Management, which are in compliance with the European Community Council Directive of November 24th, 1986 (86/609/EEC) and the International Association for the Study of Pain (IASP) Guidelines for the Use of Animals in Research.

Results and discussion

Chemistry

As a part of our continuing research to develop new, more efficient opioid analgesics, we recently prepared compounds **2**, **4** and **5** [10, 11]. Here, we report the significantly improved general synthetic procedure, as well as two novel derivatives, *cis* and *trans* 3-aminofentanyl **6**. All the compounds were prepared and used as racemates only.

Synthesis of the compounds **2** and **4** involves the Hofmann rearrangement, in the presence of *N*-bromoacetamide (NBA) and $LiOH{\cdot}H_2O$ in MeOH [10, 11]. Although the relative stability of lithium *N*-bromocarboxamide salts is known, the Hofmann rearrangement of NBA itself is base-promoted at elevated temperatures. Therefore, our original procedure involved reaction of the carboxamides at room temperature for 24–48 h, requiring about 9 and 25 equiv. of NBA and $LiOH{\cdot}H_2O$ respectively [10, 11]. Subsequently, our microwave irradiation experiments revealed a dramatic rate acceleration, with the transformation being completed within few minutes at 65 °C. However, further tests showed that it was temperature-dependent only, with the simple heating having the same effect. Thus, the reaction proceeded some 300–600 times faster at 65 °C than at 20 °C (Scheme 1). This modified protocol afforded compounds *cis*-**2**, *trans*-**2**, *cis*-**4** and *trans*-**4** in 80–90% yields, free of aryl brominated or other contaminants. Since NBA decomposition appeared insignificant, only half amount of the regents was sufficient,

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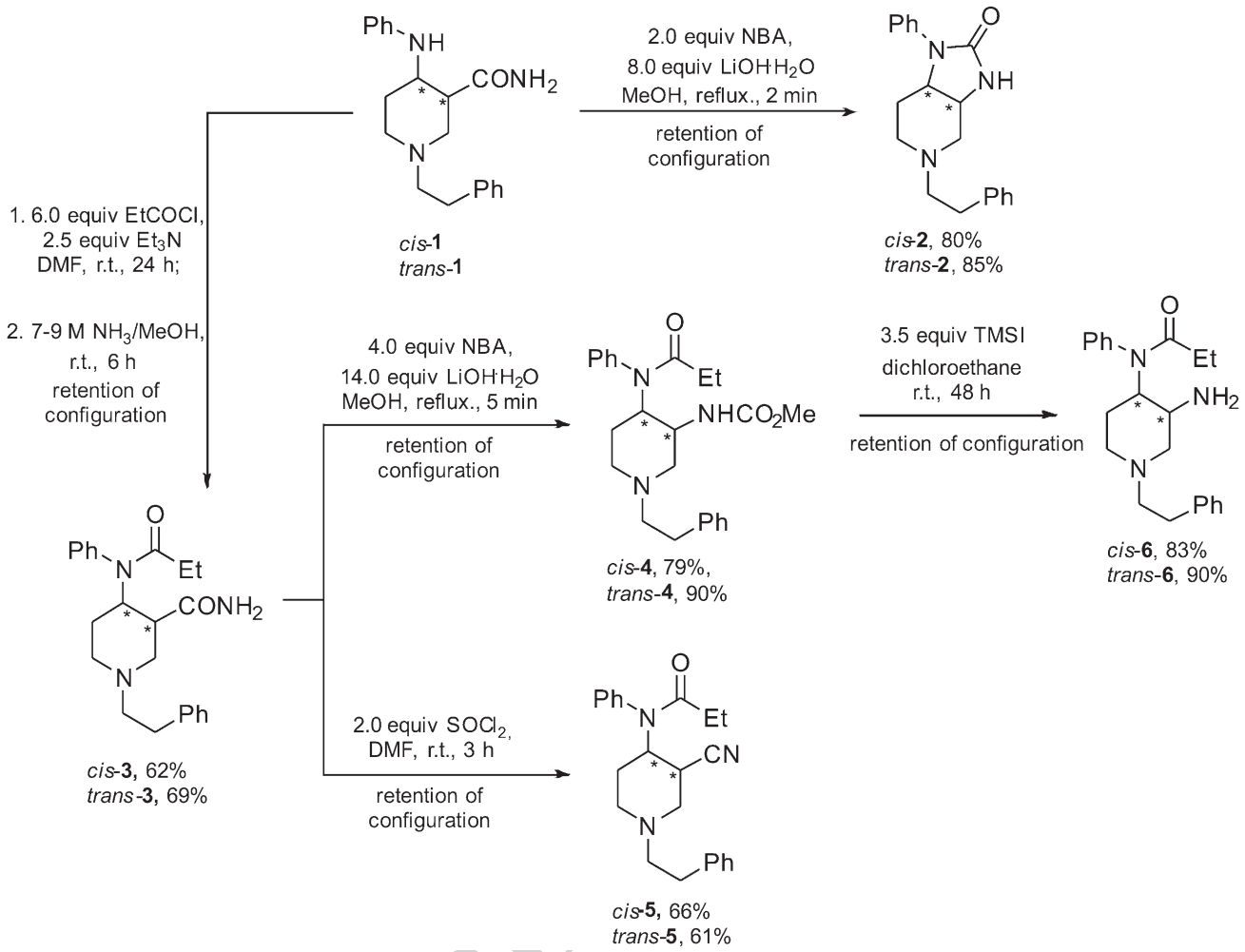

Scheme 1 Synthesis of fentanyl derivatives with nitrogen group at position C_3

compared to the original procedure. The modification is applicable to a range of diverse aliphatic and aromatic carboxamides (not shown).

We also prepared nitriles **5** by dehydration of carboxamides **3** (Scheme 1). Initial dehydration with $SOCl_2$ in toluene largely resulted in the recovered reactants. However, the reaction in DMF afforded moderate yields of *cis*-**5** and *trans*-**5** respectively, with the complete retention of configuration (Scheme 1).

Selective carbamate cleavage of *cis*-**4** and *trans*-**4** was achieved with trimethylsilyl iodide under mild reaction conditions, providing 3-amino fentanyl *cis*-**6** and *trans*-**6** in high yields, with the complete retention of configuration (Scheme 1). The reagent is particularly suitable, since it cleaves lower alkoxy groups quantitatively and selectively, while most other groups are tolerated. Also, it can be prepared inexpensively on a multi-gram scale.

In vivo antinociceptive activity of the 3-substituted fentanyl analogues 2–6

Tail-immersion test

Based on the determined ED_{50} values, the relative order of potency in tail-immersion test was found to be: fentanyl (**1**) > *cis*-**4** (0.5700) > *trans* 3-carbomethoxy fentanyl, denoted as **T**, (0.0940) > *cis*-**5** (0.0092) = *trans*-**5** (0.0090) > *trans*-**4** (0.0032) (Table 1; Fig. 1a). Compounds *cis*-**2**, *trans*-**2**, *cis*-**3**, *trans*-**3**, *cis*-**6** and *trans*-**6** did not inhibit nociception in doses up to 2 mg/kg (Table 1). Saline injection in control rats had no effect on the tail-immersion latency (Fig. 1).

It has been previously demonstrated that antinociceptive potency of the 3-substituted fentanyl analogues is predominantly influenced by the steric factors (voluminosity of the

Table 1 Summary of MPE dose–response curves, relative potency and AUC-MPE curves for compounds tested

Compound (mg/kg)	ED_{50} (mg/kg)	95% CL	Dose-response slope ± SEM	*r*	Relative potency	AUC-MPE response slope ± SEM
Fentanyl (0.0636–0.0191) *n* = 18	0.0104	0.0050 ± 0.0216	114.96 ± 14.60	0.992	1	3.59 ± 0.44
trans 3-Carbomethoxy fentanyl, **T** (0.0445–0.267) *n* = 18	0.1094	0.0856–0.1396	69.42 ± 1.80	1	0.0940 0.0684–0.1282	2.32 ± 0.09
cis-2 *n* = 3			No activity in doses up to 2 mg/kg			
trans-2 *n* = 3			No activity in doses up to 2 mg/kg			
cis-3 *n* = 3			No activity in doses up to 2 mg/kg			
trans-3 *n* = 3			No activity in doses up to 2 mg/kg			
cis-4 (0.092–0.0276) *n* = 18	0.0182	0.0132–0.0250	91.72 ± 5.01	0.999	0.5700 0.4424–0.7242	0.65 ± 0.14[a]
trans-**4** (1.84–3.68) *n* = 18	3.2382	1.6316–6.4268	103.72 ± 16.12	0.988	0.0032 0.0025–0.0041	1.95 ± 0.08
cis-5 (0.9–1.8) *n* = 18	1.1268	0.8173 ± 1.5536	122.79 ± 10.32	0.996	0.0092 0.0076–0.0113	1.55 ± 0.12
trans-5 (0.9–1.8) *n* = 18	1.1634	0.5433 ± 2.4913	147.76 ± 30.29	0.980	0.0090 0.0067–0.0123	1.49 ± 0.21
cis-6 *n* = 3			No activity in doses up to 2 mg/kg			
trans-6 *n* = 3			No activity in doses up to 2 mg/kg			

Results are summarized from data presented in Fig. 1. ED_{50}s were calculated from three doses of each compound with 6–8 rats *per* dose

n total number of animals employed to produce the respective dose–response curve, *CL* confidence limits, *r* correlation coefficient, *MPE* maximum possible antinociceptive effect, *AUC-MPE* area under the curve-maximum possible antinociceptive effect

[a]Significantly ($p < 0.05$) different in comparison with *trans* 3-carbomethoxy fentanyl. All computations were done according to Tallarida and Murray [13]

groups and *cis*/*trans* isomerism) [5, 14, 15]. For example, *cis*-3-methyl fentanyl and *cis*-3-ethyl fentanyl are about 8 and 1.5 times more potent than fentanyl, respectively. However, *trans* isomers of 3-methyl and 3-ethyl fentanyl are about 2 times more potent and equipotent to fentanyl, respectively. More voluminous alkyl groups cause a gradual drop in the activity compared to fentanyl itself [5, 8, 15, 16]. In this research, we determined that *cis*-**4**/*trans*-**4** potency ratio was 180. Also, very significantly, we found that the chemical nature of substituents critically influenced the potency. Thus, while compound **4** (with methyl carbamate substituent) is very active, compounds **3** and **6** (having carbamoyl and amino groups respectively), lack significant antinociceptive activity in doses up to 2 mg/kg. Also, 3-cyano fentanyl **5** has a very low potency compared to fentanyl, Table 1.

The antinociceptive effect of fentanyl peaked at about 15–20 min, while the equianalgesic doses of *cis*-**4**, *trans*-**4**, *cis*-**5**, *trans*-**5** and **T** peaked at about 5–10 min (Fig. 2).

Previously we have shown that 3-carbomethoxy fentanyl has a shorter duration of action than fentanyl and its duration of action is not affected by *cis*/*trans* isomerism [5]. It was assumed that the time course of action of 3-carbomethoxy fentanyl is influenced by the nature of the carbomethoxy group. In this study, *cis*-**4**, *trans*-**4**, *cis*-**5** and *trans*-**5** also showed shorter duration of action (Fig. 1) than fentanyl, as indicated by lower AUC-MPE response slopes (Fig. 2b; Table 1). These differences were not statistically significant ($p > 0.05$). However, the duration of action of *cis*-**4** was statistically ($p < 0.05$) shorter than that of (±) *trans* 3-carbomethoxy fentanyl (T) (Fig. 2b; Table 1).

The antinociceptive activity of $4ED_{50}$ of each of the compound tested was abolished by subcutaneous naloxone hydrochloride (0.1 mg/kg; s.c; Fig. 1) indicating that the effect is mediated via opioid receptors.

Formalin test

Injection of formalin into the hind paw results in a biphasic pain behavior; the first phase results from direct effect of formalin on nociceptors, whereas the second phase represents tissue injury. Thus, more central pain processing mechanisms are involved in the establishment of chronic neuropathic or inflammatory pain [17, 18].

In the present study we compared fentanyl and *cis*-**4** in two different types of nociceptive tests: tonic (formalin-induced inflammation) and phasic (tail-immersion). Our results indicate that fentanyl and *cis*-**4** are effective antinociceptive agents in the both tests and their effects are dose-dependent (Fig. 2a, c). We found that fentanyl is about 10 times less potent in formalin test then in tail-immersion test ($ED_{50} = 0.1021$ vs $ED_{50} = 0.0104$), in close agreement with one literature report [19]. However,

Journal : Large 43440 | Article No : 121 | Pages : 7 | MS Code : 121 | Dispatch : 29-6-2020

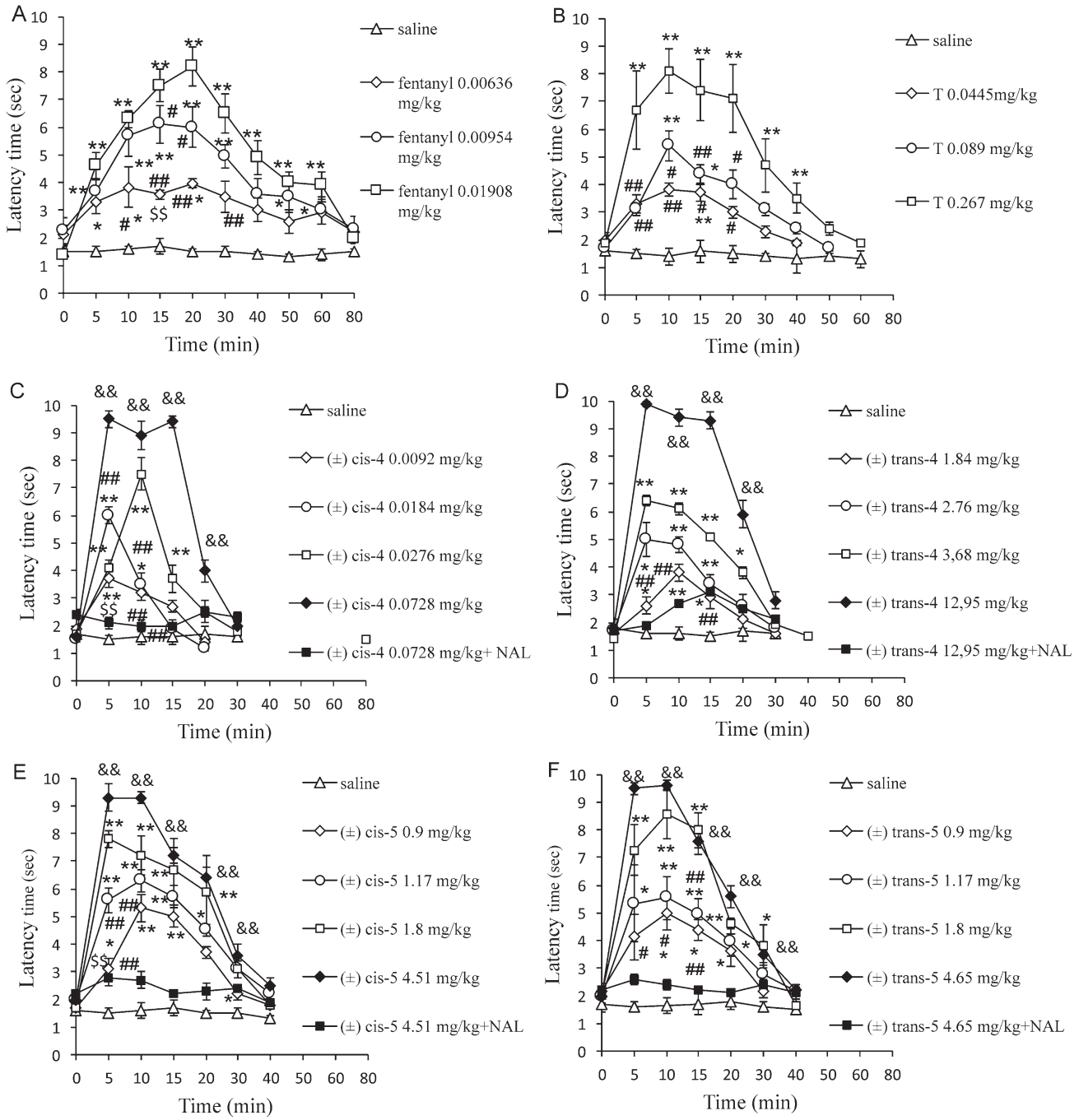

Fig. 1 The time-response curves on the tail-immersion for fentanyl (**a**), *trans* 3-carbomethoxy fentanyl (**b**), *cis*-**4** (**c**), *trans*-**4** (**d**), *cis*-**5** (**e**), and *trans*-**5** (**f**) given i.p. in rats and the antagonism with naloxone. Each point represents the mean ± SEM of the antinociception in six to eight rats. At each time interval the differences between the corresponding means were verified using the one-way analysis of variance (ANOVA), followed by Tukey's HSD post hoc test where statistical significance was determined by comparing with the control (0.9% NaCl) ($^{*}p<0.05$, $^{**}p<0.01$), **a** comparing with the fentanyl 0.01908 mg/kg ($^{\#}p<0.05$, $^{\#\#}p<0.01$), **b** comparing with *trans* 3-carbomethoxy fentanyl 0.267 mg/kg ($^{\#}p<0.05$, $^{\#\#}p<0.01$), **c** comparing with the *cis*-**4** 0.0276 mg/kg ($^{\#}p<0.05$, $^{\#\#}p<0.01$); *cis*-**4** 0.0184 mg/kg ($^{\$}p<0.05$, $^{\$\$}p<0.01$); **d** comparing with the *tans*-**4** 3.68 mg/kg ($^{\#}p<0.05$, $^{\#\#}p<0.01$), **e** comparing with the *cis*-**5** 1.8 mg/kg ($^{\#}p<0.05$, $^{\#\#}p<0.01$); *cis*-**5** 1.17 mg/kg ($^{\$}p<0.05$, $^{\$\$}p<0.01$), **f** comparing with the *trans*-**5** 1.8 mg/kg ($^{\#}p<0.05$, $^{\#\#}p<0.01$). **c**–**f** The differences between $4ED_{50}$ and $4ED_{50}$ + naloxone was verified using the *t* test for unpaired values ($^{\&}p<0.05$, $^{\&\&}p<0.01$). The mean ± SEM of latencies before and 10 min after saline injection were found to be: 1.6 ± 0.1 and 1.5 ± 0.3 s, respectively ($p<0.0$, *t test for paired values*; **a**), 1.6 ± 0.1 and 1.5 ± 0.2 s, respectively ($p<0.05$; **b**), 1.7 ± 0.2 and 1.6 ± 0.3 s, respectively ($p<0.05$; **c**), 1.8 ± 0.3 and 1.6 ± 0.3 s, respectively ($p<0.05$; **d**), 1.6 ± 0.2 and 1.6 ± 0.3 s, respectively ($p<0.05$; **e**) and 1.7 ± 0.3 and 1.7 ± 0.3 s, respectively ($p<0.05$; **f**)

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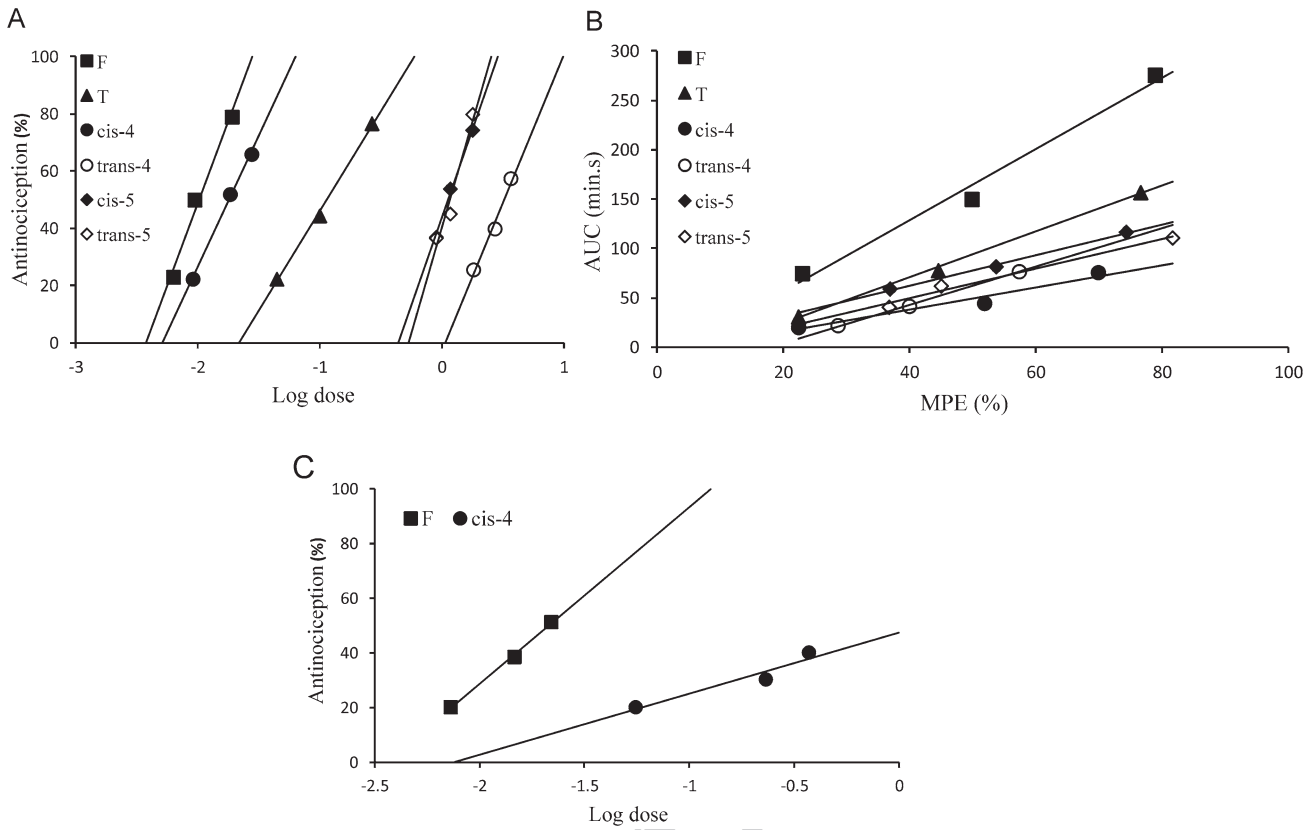

Fig. 2 The log dose–response curves (**a**) and AUC-MPE curves (**b**) on the tail-immersion for compounds tested; the log dose–response curves on the formalin test for compounds tested (**c**). Each point represents the mean ± SEM of the antinociception in six to eight rats. Dose–response slopes ± SEM for fentanyl and *cis*-**4** are 64.62 ± 2.9 and 22.57 ± 6.5, respectively. Correlation coefficients (*r*) for fentanyl and *cis*-**4** are 0.99 and 0.96, respectively

other researches clamed that the opioid agonists such as morphine, meperidine, and fentanyl are more potent in the tonic test than in the phasic tests [20]. In the present study, formalin test revealed that ED_{50} of *cis*-**4** was 1.3090 mg/kg, some 70 times higher than the ED_{50} in tail-immersion test. Therefore, fentanyl and *cis*-**4** are about 10 and 70 times less potent in formalin than in tail-immersion test, respectively. This difference in potency could be attributed to neuroanatomical and biochemical mechanism variations, involving phasic and tonic pain. However, drawing any solid conclusions would require additional experiments.

Fentanyl is commonly used for the management of both acute and chronic pain [21]. Like fentanyl, compound *cis*-**4** is characterized by high potency, rapid beginning and short duration of action and due to this might be incorporated in different pharmaceutical forms. Further studies should evaluate tolerability and safety of this series of novel fentanyl analogs and compare them with fentanyl [3].

Conclusions

The optimized synthetic route towards fentanyl analogs bearing nitrogen groups in position C_3 of piperidine ring is presented herein. Ten compounds were tested in vivo for their antinociceptive activity. Compound *cis*-**4** showed pharmacological behavior similar to fentanyl. It is characterized by high potency, rapid onset and short duration of action. Therefore, it has potential to be incorporated in different pharmaceutical forms. Further studies should evaluate tolerability and safety of this series of novel fentanyl analogs and compare them to fentanyl [3].

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Compliance with ethical standards

Conflict of interest Authors declare that there are no conflicts of interest.

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