Anti-allodynic effects of a novel quinazolin-4(3H)-ones derivative: 2-(2-methyl-4-oxoquinazolin-3(4H)-yl)-N-p-tolylacetamide (P-TOL) in CCI and SNL induced neuropathic pain in rats.

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Abstract— Quinazoline-4(3H)-ones and its derivatives are versatile nitrogen heterocyclic compounds and exhibit potent activities like analgesic and anti-inflammatory. Here we have investigated anti-allodynic potentials of some of the newly synthesized Quinazolines derivative. Pharmacological activity was evaluated in the rodent models of neuropathic pain (Chronic constriction injury and spinal nerve ligation). The compound T-02 (P-Tol) demonstrated good activity in neuropathic pain models.

In Chronic constriction injury (CCI) the loose ligation of the sciatic nerve model, the compound T-02 (P-Tol) shows the significant effect at doses 3 mg/kg and 10 mg/kg when administered orally. The standard Gabapentin also shows the significant reduction in pain at dose 150 mg/kg after the oral administration. In spinal nerve ligation (SNL), the tight ligation to the L5 and L6 nerve, the compound T-02 (P-Tol) after oral administration we have not seen any significant reduction at low dose 1 mg/kg and 3 mg/kg. But at high dose 10 mg/kg compound shows the significant reduction in pain. The standard Gabapentin also shows the significant effect at dose 150 mg/kg.

The results in present study demonstrate that the compound shows the remarkable effect on neuropathic pain. The effect of compound in CCI model shows more significant as compare to the SNL model of neuropathic pain. This may be due to the sensitivity produced by nerve damage.

Key words: Quinazolines, analgesic, anti-inflammatory, chronic constriction injury, spinal nerve ligation, anti-allodynic.

1 Introduction

IASP (International Association for the Study of Pain) has recently published a new definition of neuropathic pain according to which neuropathic pain is defined as ''pain caused by a lesion or disease of the somatosensory system'' (1). It is tough to describe exactly what pain is, despite the fact that individual know what he means to say. Pain is an undeviating reaction to an inconvenient experience associated with tissue damage, such as injury, inflammation or diseased condition. Whereas as rigorous pain occurs spontaneously due to evident influence of different source or persist long even after the injury has healed (e.g. trigeminal neuralgia, phantom limb pain), also in conditions such as brain or nerve injury (e.g. following a stroke or herpes infection).

Agonizing circumstances such as brain or nerve injury, are disparate to tissue injury, and often depicted as 'neuropathic pain'. Neuropathic Pain is especially universal and a major cause for disability and distress, and dose not respond much to conventional analgesic drugs, NSAID's even though the immediate cause is clear. In normal conditions the primary afferent fibres of peripheral nerves which are usually small in diameter (C and Aδ) are linked with pain signal. These nociceptor or sensory nerve endings in peripheral tissues are stimulated by diverse kind of peripheral stimuli such as mechanical, chemical and thermal (2) further the signal are transmitted to spinal cord and brain, as a result the path of action is called as nocieption and further lead to the perception of pain.

The nociceptors have two different types of axons C and Aδ fibers, that transmit the nociceptive information from muscle and viscera as well as from the skin ,unmyleinated (C) fibres axon also referred as slow transmitting is associated with polymodal nociceptive endings express a monotonous, scatter, burning pain sensation whereas myelinated (Aδ) fibres transmit sharp, well-localized reaction of pain.

It is observed that due to tissue injury there are numerous pathological changes, and a variety of chemicals are released locally, which act on nerve terminals which directly or facilitate in enhancing the sensitivity to different stimuli.

Neuropathic pain is not a single disease, but a syndrome caused by a range of different diseases and lesions, which manifests as an array of symptoms and signs. The mechanisms underlying these different conditions are multiple. Some of the mechanisms are known, but many are not. Increased understanding of pain mechanisms should put us in a better position to treat patients and design rational treatment strategies. (3)

The current therapy for neuropathic pain is not satisfactory; more than two-thirds of neuropathic pain patient's receive insufficient pain relief, and this poor response is likely related

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to our failure to target relevant pain-generating mechanisms in individual patients. (4). Antidepressants and gabapentinoids (Gabapentin and Pregabalin) with an approved indication for neuropathic pain are nonspecific compounds with a general action on neuronal hyper excitability. As neuronal hyper excitability is a mechanism shared by many chronic pain conditions, treatment with antidepressants and gabapentinoids should definitely not be withheld from patients (3). As testified in earlier studies the novel compound 2-(2-methyl-4-oxoquinazolin-3(4H)-yl)-N-p-tolylacetamide.(P-Tol)T-02 showed significant anti inflammatory and anti-hyperalgesic effect in rodent models of inflammatory pain (5). These findings prompted us towards evaluation of novel compound (P-Tol) T-02 in different neuropathic pain models. The experimental animal models used to study neuropathic pain are

1. Spinal nerve ligature (SNL) –L5 & L6 spinal nerves innervating the hind paw are ligated tightly.
2. Partial sciatic nerve ligature (PSL) –half to two third part of the sciatic nerve is ligated tightly.
3. Chronic Constrictive Injury (CCI) – includes the placement of four loose ligatures on the sciatic nerve tightened by using chromic catgut.

Other methods include the intraperitoneal or intravenous injection of streptozocin (diabetic neuropathic pain) or paclitaxel or vincristine (chemotherapy induced neuropathic pain). Animal models of central pain are contusion (trauma using the force of impact of tissue dislocation), or ischemic lesions from slow compression by clamping or balloon insufflation. Cytotoxic methods use injections of glutamate analogues (cainate) or substances that cause lesion in specific areas of the gray matter. The techniques described are aimed at causing mechanical and thermal Hyperalgesia. (6, 7)

The intense search for biologically active substances in quninazoline series began earlier in this century. Febrifugine, a quinazolinone alkaloid, was first isolated from Chinese plant aseru (Dichroa febrifuga Lour) later also found in garden plant Hydrangea, has a potential anti-malarial activity this dole out an drive for investigation of the research on quinazolines. Quinazolines and some of condensed quinazolines exhibit potent analgesic, anti-inflammatory activities (8). Quinazolin-4(3H) - ones with 2, 3-disubstitution is reported to possess potent analgesic, anti-inflammatory and anticonvulsant activities (9, 10). Quinazolone derivatives are synthesized starting from anthranilic acid moiety with appropriate substituent in order to have a specific substituent in three to four steps. Based on the substitution pattern in different positions of quinazolone derivatives, they are classified as (a) di-substituted, (b) tri-substituted, (c) tetra-substituted, (d) 1, 2-fused, (e) 2, 3-fused and (f) 3, 4-fused derivatives. 2-substituted quinazoline derivatives possess multiple therapeutic activities like anti-allergic, PDE 2 inhibitor, PDE 5 inhibitors (11) analgesic, and anti-inflammatory (12).The title compounds 2-(2-methyl-4-oxoquinazolin-3(4H)-yl)-N-p-tolylacetamide were prepared from an anthranilic acid or its derivative, formation of 2-alkyl-4(3H) quinazolinone by condensation of anthranilic acid or substituted anthranilic acid and amides as designated in the Niementowski reaction (13).

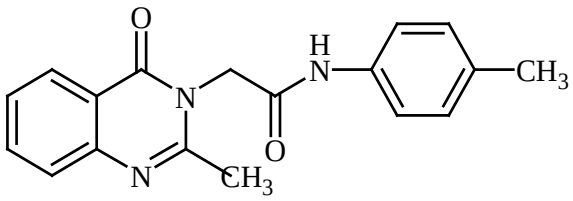

Fig. 1 T-02 (P-Tol) 2-(2-methyl-4-oxoquinazolin-3 (4H)-yl)-N-p-tolylacetamide

There are no promising quinazolines available in the market. Except few drugs like Proquazone, Afloqualone, Diproqualone (14, 15), fluproquazone (16) having potent analgesic and anti inflammatory actions with minimal gastric ulceration. Two of the most frequently used rodent models are CCI and SNL were used in our study to assess anti- allodynic potential of our novel compound 2-(2-methyl-4-oxoquinazolin-3(4H)-yl)-N-p-tolylacetamide as based on previous studies and illustrated properties.

So, present study was undertaken to investigate pharmacological effect of newly synthesized Quinazolinone derivative in the animal models of neuropathic pain in male Sprague Dawley rats.

2. MATERIALS AND METHODS

2.1 Chemicals and materials

Gabapentin (Fluorochem, Derbyshire, United Kingdom), Isoflurane (Abbott, Mumbai, India), Silk suture, Catgut 5-0

2.2 Compounds

The test compound and standard were dissolved in 0.5% Tween-80+0.5% carboxyl methyl cellulose solution for oral administration. The test compound was dissolved in 10% DMSO, 10% Cremophor and 80% saline for intravenous administration

2.3 Animals and experimental design

2.3.1 Animals

Adult male S.D Rats: 7-9 Weeks of age and body weight (210-250g) were procured from Laxmi Biofarms Pvt. Ltd. Ale Phata, Pune. Animals were maintained at a constant temperature (22^0 C) and had free access to food and drinking water in a 12 hr light/dark cycle with lights on from 06:30 to 18:30 h. All experimental procedures were performed under the guidelines of Institutional Animal Ethics Committee.

2.3.2 In vivo pharmacokinetic profile of T-02

Male S.D Rats: 7-9 Weeks of age and body weight (210-250g) fasted overnight and were administered T-02 intravenously at 1 mg/kg dose and orally at 3 mg/kg dose. Blood samples following intravenous dosing were collected at 7 min, 15 min, 30 min, 1, 2, 4, 8 and 24 h post dose (8 time points). Following oral dosing, blood samples were collected at 15 min, 30 min, 1, 2, 4, 8 and 24 h post dose (7 time points). Plasma samples were analyzed by LC-MS/MS following protein precipitation with acetonitrile containing internal standard as described earlier (5).

2.3.3 In vivo efficacy of T-02 in neuropathic pain Chronic

Constriction Injury (CCI)

The anti-allodynic activity was carried out in SD rats. Non fasted animals were weighed and operated. Chronic constriction injury was performed as described by Bennett. All surgical procedures were carried out under sterile conditions. Briefly, rats were anaesthetized with isoflurane (2.5% in Oxygen). The left common sciatic nerve was exposed at the middle of the thigh by blunt dissection through biceps femoris. Proximal to the sciatic trifurcation, about 7 mm of nerve was freed of adhering tissue and 4 loose ligatures (chromic cat gut 5-0, Ethicon, Johnson & Johnson) were tied loosely around sciatic nerve with about 1 mm spacing. The ligatures were loosely tied in order to minimize nerve constriction. After surgery, the skin was closed by double knots with the use of surgical thread (3-0, Ethicon, Johnson & Johnson) (17).

Behavioral tests:

Measurement of mechanical allodynia

Mechanical allodynia was measured at day 14 post surgery by using previously described Up-down method as described previously, von Frey filaments (Bioseb, France) were used to assess mechanical allodynia. The animals were placed in a plexiglass cage (16 x 24 x 14 cm) with a grid bottom and adapted for at least 10 minutes. Mechanical stimuli were generated by touching the plantar region of the left hind paw of the rat with a continuous increasing/decreasing pressure changes by the pattern of (xoxoxo). For the paw withdrawal threshold the mean of two independent measurements was calculated. Filaments used in experiment were 3.61, 3.84, 4.08, 4.31, 4.56, 4.74, 4.93 and 5.18 g. The values of the paw withdrawal thresholds were manually recorded and noted in result sheet (18).

The basal value was recorded and selected animals were divided into five groups (n=6). Group I and II were administered with normal saline (2 ml/kg, PO) and Gabapentin (150 mg/kg, PO) respectivly, while remaining groups were treated with T-02 (1, 3 and 10 mg/kg, PO). Post 60 min. of dosing animals were taken for observation. The observer was blinded to pharmacological treatments.

The % MPE was calculated by using following formula,

% MPE = ((Log PWT-Avg. Log PWT of vehicle)/ (Log (15) - Avg. Log PWT of vehicle))*100

2.3.4 In vivo efficacy of T-02 in neuropathic pain Spinal nerve ligation (SNL)

The allodynic activity was carried out in SD rats. Non fasted animals were weighed and operated. L5-L6 ligation was performed according to the method of Chung. All surgical procedures were carried out under sterile conditions. Rats were anaesthetized with isoflurane (2.5% in Oxygen).The rat was placed in a prone position and the left paraspinal muscles were separated from the spinous processes at the L4-S2, levels. The L6 transverse process was carefully removed with a small rongeur to identify visually the L4-L6 spinal nerves. The left L5 and L6, spinal nerves were isolated and tightly ligated with 5-0 silk thread. A complete hemostasis was confirmed and the wound was sutured (19). The behavioral testing was done by using Up-down method as described in previous model.

The basal value was recorded at 14 day post surgery and selected animals were divided into five groups (n=6). Group I and II were administered with normal saline (2 ml/kg, PO) and Gabapentin (150 mg/kg, PO) respectively, while remaining groups were treated with T-02 (1, 3 and 10 mg/kg, PO). Post 60 min. of dosing animals were taken for observation. The observer was blinded to pharmacological treatments.

The % MPE was calculated by using following formula,

% MPE = ((Log PWT-Avg. Log PWT of vehicle)/ (Log (15) - Avg. Log PWT of vehicle))*100

2.4 Statistical analysis

One-way analysis of variance followed by Dunnett post test (ANOVA; Graph Pad PRISM®, Version 4.0, San Diego, CA, USA) was applied to determine significant differences between the groups. A value of $P<0.05$ was considered significant. The pharmacokinetic parameters were calculated by a non-compartmental method with Win Nolin professional Version 4.1.

3. RESULTS

3.1 In vivo pharmacokinetic profile of T-02

The pharmacokinetics of T-02 (P-Tol) was evaluated in SD rats The PK profile of Test Compound T-02 (P-TOL) following PO administration was observed, maximum plasma concentration (C_{max}) achieved at 0.58 ± 0.38 h (tmax) and the terminal half-life ($t_{1/2}$) was found to be 2.52±0.09 h. Following IV administration, elimination half life ($t_{1/2}$) was found to be 2.52 ± 0.09 h and clearance was ~ 115.69 ± 13.04 mL/min/Kg. The absolute oral bioavailability (%F) was 84 %.

Compound	**T-02**				
Route		**IV**		**PO**	
Dose	(mg/kg)	**1**		**3**	
Tmax	(h)	-	-	0.58	±0.38
Cmax or C0	(ng/mL)	194.13	±22.50	199.65	±33.71
AUClast	(ng.h/mL)	139.14	±15.71	351.32	±57.87
AUCinf	(ng.h/mL)	145.65	±16.75	356.02	±56.90
T1/2	(h)	2.52	±0.09	-	-
Vd	(L/kg)	11	±0.75	-	-
CL	(mL/min/kg)	115.69	±13.04	-	-
% F	84				

Table 1 Pharmacokinetic Parameters of T-02 (P-TOL) in Sprague Dawley Rat

3.2 Effect of T-02 on neuropathic pain (CCI)

The compound T-02 (P-Tol) was initially evaluated with the goal of proving the effect of compound on neuropathic pain; we found that the oral administration of compound shows significant results. The compound T-02 (P-Tol) (1, 3 and 10 mg/kg P.O.) shows significant dose dependent increased PWT and % MPE (Fig 2/Table 2) in the model of neuropathic pain.

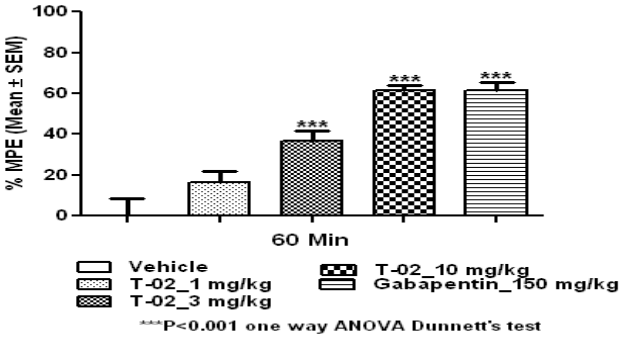

Fig 2 Effect of T-02 (P-TOL) on CCI induced neuropathic pain in Sprague Dawley Rat

Treatment	%MPE @ 60 min			
	Mean	SEM	SD	N
Vehicle	0	9	21	6
T-02_1 mg/kg	17	5	13	6
T-02_3 mg/kg	37	5	12	6
T-02_10 mg/kg	61	2	6	6
Gabapentin_150 mg/kg	61	4	10	6

Table 2 Effect of T-02 (P-TOL) on CCI induced neuropathic pain in Sprague Dawley Rat

3.3 Effect of T-02 on neuropathic pain (SNL)

In the present study, it has been demonstrated that acute oral administration of the T-02 (P-Tol) compound, reduces the mechanical hyperalgesia associated with a neuropathic pain model. In similar Gabapentin also reduced hyperalgesia. The results in (Fig 3) indicate that the administration of T-02 (P-Tol) (1, 3 and 10 mg/kg P.O.) significantly reduced Mechanical hyperalgesia at high dose 10 mg/kg (Table 3). These findings suggest that compound T-02 (P-Tol) may provide a novel approach for relieving neuropathic pain.

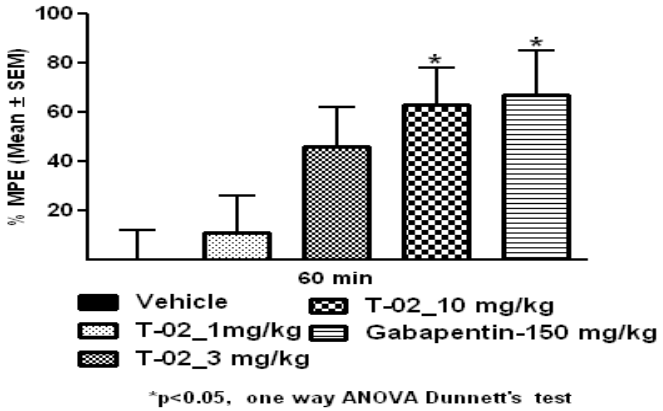

Fig 3 Effect of T-02 (P-TOL) on SNL induced neuropathic pain in Sprague Dawley Rat

Treatment	%MPE @ 60 min			
	Mean	SEM	SD	N
Vehicle	0	12	30	8
T-02_1 mg/kg	11	15	42	8
T-02_3 mg/kg	46	16	46	8
T-02_10 mg/kg	63	15	42	8
Gabapentin_150 mg/kg	67	18	51	8

Table 3 Effect of T-02 (P-TOL) on SNL induced neuropathic pain in Sprague Dawley Rat

4. DISCUSSION

The Chronic constriction injury model is widely used to assess the effect of drugs on peripheral neuropathic pain. The CCI model consist of loose ligation of the sciatic nerve at mid thigh level with chromic gut suture. An inflammatory reaction develops in response to the catgut and consequently causes a loss of most A-fibers and some C-fibers, but few cell bodies. After the ligation of sciatic nerve there is alteration in the expression of Sodium channels in the cell bodies and the terminal neuroma of peripheral nerves. Sodium channels are not only voltage-gated channels, which are altered following peripheral nerve injury. Calcium channels have also been shown to influence the generation of hyperalgesia and allodynia (20). Peripheral nerve injury triggers the recruitment of circulating inflammatory cells. Infiltrated neutrophils in injured nerves play an important role in early stages of neuropathic pain through the release of pro-inflammatory mediators, such as cytokines TNF-α, IL-1β and IL-6 and reactive oxygen species, which are involved in regulating neuronal excitability .In addition, neutrophils have a significant impact on subsequent macrophage infiltration to the injured nerves by secreting chemokines/cytokines MIP-1α, MIP-1β and IL-1β (21).

The SNL model was conducted to examine cellular responses to injury at the DRG level as the L5 and L6 DRGs will be affected and this allowed investigation into the importance of input from uninjured afferents in neuropathic pain. In normal primary afferent neurons, it is rare for firing threshold to be reached without the inputs of stimulus. However, following a nerve injury, it has been demonstrated that there is a large increase in the level of spontaneous firing in the afferent neurons linked to the injury site. This has been termed ectopic discharge and has also been demonstrated in humans, suffering from neuropathic pain. A sodium channel has played a very critical role in generation of ectopic firing. Sodium channels are critical to the physiology of excitable membranes, including neuronal membranes. One important finding of potential significance to the generation of ectopic firing is alterations in the expression of sodium channels in the cell bodies and the terminal neuroma of peripheral nerves following nerve injury (22). Like most neurons, sensory neurons in DRG are supported by a cast of other cells. In the DRG these supportive cells are satellite glial cells (SGC), dendritic cells, macrophages, and endothelial cells. Activation of SGCs results in increased glial fibrillary acidic protein (GFAP) expression and release of pro-inflammatory cytokines, for example, TNFα and

IL-1β (23). These cytokines released by activated SGCs have excitatory actions on nociceptive neurons (24). In spinal nerve ligation (SNL) injured rats; GFAP expression peaks at one day after nerve injury, and is still present 10 days after (25). Anti-allodynic effect of T-02 (P-Tol) in CCI & SNL could be due to the antagonist effect on Sodium or Calcium channels or may be due to inhibition of pro-inflammatory mediators as reported in earlier studies of inflammatory pain models(5). The present study strongly avowed that the anti-allodynic activity of new derivative of Quinazoline 2-(2-methyl-4-oxoquinazolin-3(4H)-yl)-N-p-tolylacetamide in neuropathic pain models of Bennett and Chung.

To summarize the present work, we would like to state that newly synthesized 2-methyl -3- substituted oxoquinazolin derivative demonstrated good activity in neuropathic pain. The further studies should be initiated to know exact mechanism of action in different pain or diseased pain condition.

5. ACKNOWLEDGMENT

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