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Original Article

Synthesis and Antinociceptive Activity of 5-Amino (*N*-Substitutedcarboxamide)quinoline Derivatives Targeting TRPV1 Receptor

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ABSTRACT

Background: Quinoline is a significant heterocyclic moiety involved in several biological activities including inhibition of transient receptor potential vanilloid 1. **Materials and Methods:** A series of 5-amino(*N*-substituted carboxamide)quinoline derivatives (2o-2t) were synthesized through two steps. FT-IR, ^{1}H NMR and mass spectrum techniques were used to confirm these obtained derivatives. Using acetic acid-induced writhing in rats, all the compounds were tested for TRPV1 inhibition by antinociceptive action. The stomach tissue was investigated by histopathology for checking the ability of synthesized derivatives to damage the stomach mucosa. Also, the biochemical analysis of blood serum was carried out to check the nephrotoxicity and hepatotoxicity. **Results:** All the derivatives (2o-2t) having the dose of 200 mg/kg gave good TRPV1 inhibition by antinociceptive activity. Among all, the derivatives 2q, 2r and 2s had a percentage inhibition of 43.90%, 34.15% and 39.04% respectively when compared with a dose of 100 mg/kg of Ibuprofen (48.78%). **Conclusion:** A novel 5-amino (*N*-substituted carboxamide) quinoline compounds are shown to be an intriguing place to start for further investigation into potent and reliable TRPV1 inhibitors.

Keywords: Quinoline, Antinociceptive, TRPV1, Acetic acid, Histopathology.

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INTRODUCTION

A crucial pain detector and integrator, the Transient Receptor Potential Vanilloid 1 (TRPV1) was originally cloned and reported in 1997. It comprises a not selective ion channel activated in early sensory nerve cells.[1] The various stimuli activate it. The stimuli included exogenous substances (resiniferatoxin or capsaicin), endogenous compounds (oxidative metabolites of linoleic acid and anandamide), acids having pH less than 6.8 and temperature (greater than 43°C).[2-5] The primary sensory axons of peptidergic sensitive neurons, such as the sparsely A-δ myelinated and C-fibres unmyelinated, are where TRPV1 receptors are most abundantly expressed. Non-neuronal cells have also been shown to contain TRPV1 receptors.[6] The activation of the ion channel has been linked to peripheral nerve damage and persistent painful inflammation.[7] In light of its important function in several disorders, such as neuropathic discomfort, inflammation in joints and bowel inflammation, others as well, TRPV1 has been regarded as being a pro-inflammatory channel.[8,9] In various types of both inflammatory as well as neurological pain, pharmacological inhibition of the receptor produced antinociceptive effectiveness. It was demonstrated by the development of multiple powerful and effective small compound TRPV1 inhibitors during over ten years.[10-12] However, a hurdle that prevented several TRPV1 antagonists from moving forward with clinical trials was their propensity to cause hyperthermia adverse effects within preclinical studies. Due to this, the main difficulty in creating antagonists of TRPV1 for the management of pain was the biological separation of hyperthermic and antinociceptive properties.[13] By using some literature that made use of the synthetic processes and biological functions of the quinoline scaffold, numerous chemists from all over the world expounded on the significant role that quinoline and its derivatives play in science.[14-20] The six-membered fused heterocycle with nitrogen as a heteroatom is termed quinoline or benzo[*b*]pyridine.[21] Additionally, the quinoline ring structure is found in many different natural molecules, particularly within alkaloids. It is rarely employed in the design of several synthetic substances with different biological effects like anti-fungal, anti-bacterial, anti-cancer, CNS effects, cardiovascular, antioxidant, analgesic, anti-convulsant, anti-inflammatory, anti-mycobacterial, anti-malarial, anti-protozoal, anti-viral, anthelmintic and other activities.[22-26] The quinoline framework

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has emerged a new template for the creation and identification of novel antinociceptive agents. The number of substituents on the quinoline ring or compounds with a quinoline ring fused to other heterocycles determines the classification of these agents. Additionally, this heterocycle has drawn special attention because of its wide range of pharmacological characteristics, which include its capacity to target many inflammatory triggers. These include Transient Receptor Potential Vanilloid 1 (TRPV1) antagonist, Phosphodiesterase 4 (PDE4), inhibitors of Cyclooxygenase-2 (COX-2) and Tumour Necrosis Factor (TNF)-α Converting Enzyme (TACE).[27] Many monosubstituted quinolines have been reported as TRPV1 antagonist.[28-30] Taking all of this into account, certain quinoline derivatives are here synthesized and their spectroscopic confirmation is provided. The biological effects of the synthesized compounds that target the TRPV1 receptor are also examined.

MATERIALS AND METHODS

Materials

The required solvents as well as reagents were all bought commercially through TCI chemicals, Spectrochem and S.D. Fine chemicals. By determining the melting point and purity using TLC, when a single spot was seen, the identity of all the compounds was confirmed. For monitoring the reactions, on precoated silica gel plates (DC Kieselgel 60, F_{254}, E. Merck, Germany) employing hexane: methanol (8:2) solvent mixture, Thin-Layer Chromatography (TLC) was performed. A scientific melting point device was utilized for measuring melting points. On a Shimadzu IR affinity-1S and Drs 8000 spectrophotometer, the IR spectra of the substances have been recorded and the representative absorption bands were presented. DMSO was used as a solvent for the ^{1}H NMR spectra. For this, the Bruker AV 500 MHz was used with internal Tetramethylsilane (TMS) as standard. On an LC-MS-QTOF-6540 instrument, Electron Spray Ionization Mass Spectra (ESI-MS) were used to calculate the molecular masses.

Methods

Synthetic Procedure for 5-amino(*N*-substituted carboxamide)quinoline derivatives[31,32]

Step I: Preparation of intermediate *i.e.,* 2,2,2-trichloro-*N*-quinolin-5-yl-acetamide

The mixture of 1.0 g 5-amino quinoline, 40 mL dichloromethane and 1 mL triethylamine was prepared. It was cooled at 5°C. To this, 1.38 g trichloroacetyl chloride was added dropwise. Then this solution was concentrated. The dilution of the resulting concentrate was done with ethyl acetate. After the dilution, it was agitated at room temperature for 14 hr. Hydrochloric acid (1N) was used for cleaning the solution and separating an aqueous layer. An aq. Sodium bicarbonate was used for treating separated layers and extraction was done by using ethyl acetate. The next step was to combine organic phases, then concentrate and wash with water. The solid leftover has been suspended with ethyl acetate and filtered to produce an intermediate.

Step II: Preparation of 5-amino (*N*-substituted carboxamide)quinoline derivatives

A mixture containing 0.502 g 2,2,2-trichloro-*N*-quinolin-5-yl-acetamide, corresponding amine (1.83 mmol), 0.65 mL diazabicycloundecene and 10 mL acetonitrile refluxed for 3 hr. Then, it was cooled. After cooling, the mixture was concentrated and diluted using ethyl acetate. Aqueous ammonium chloride was employed for washing the diluted concentrate. The next step was to separate an organic layer and concentrate it under a vacuum. The concentrate that remained in ethyl acetate was filtered to get the product as a tan solid.

Biological Evaluation

Ethical Considerations

The conduct of the study was authorized by the Department's Institute Animal Ethics Committee (Sanction Letter No. IAEC/UDPS/2021/03 dated 27/12/2021).

Animals

The Rashtrasant Tukadoji Maharaj Nagpur University's Animal Research Centre in Nagpur provided the Wistar rats (180-250 g), which were used in this study. All animals spent 7 days getting acclimated to the lab environment before the experiments began. Rats were kept in polypropylene cages lined with husks. The animals were kept in a setting that alternated between 12 hr of light and 12 hr of darkness, both of which were set at 24±1°C and 55±15% relative humidity. Regular animal food and unlimited water were supplied to the rats.

Drugs

Ibuprofen was used as the standard drug for the study. It was procured from TCI Chemicals (India) Pvt. Ltd.

Study Protocol of TRPV1 Inhibition by Antinociceptive Activity

Following seven days of adapting, the animals were grouped into eight sets of six randomly, in this order:

- One set pretreated orally having a normal saline solution (control group, C);
- One set had pretreatment of standard Ibuprofen (100 mg/kg b. wt.) intraperitoneally.33,34
- Six sets pretreated orally with 200 mg/kg b. wt. of compounds 2o, 2p, 2q, 2r, 2s and 2t.

Antinociceptive activity for TRPV1 Inhibition by Acetic acid-induced writhing test[35-37]

The animal sets were pretreated orally with control, 2o, 2p, 2q, 2r, 2s and 2t and intraperitoneally with standard Ibuprofen. After 30 min, acetic acid (0.6%) was administered intra-peritoneal to each of the animals of all the groups (10 mL/kg b. wt.). Amounts of writhing or stretching were counted for 5 to 30 min after giving an injection of acetic acid. Then the number of writhing of the test sample was compared relative to control and standard groups. The evaluation of antinociceptive activity was expressed as the percentage reduction or inhibition of the total abdominal writhes by using the formula below:

$$\text{Percentage Inhibition} = [\text{No. of writhes in control} - \text{No. of writhes in test}] / \text{No. of writhes in control} \times 100$$

After completion of the test, blood was drawn from the retro-orbital plexus for biochemical assays. Injection of thiopental sodium was used intraperitoneally for sacrificing the rats and immediately dissected the specimens of the stomach. The stomach was then carefully opened along its greater curvature, gently dipped in normal saline to remove any remaining contents, macroscopically inspected and preserved in 10% formalin for histological processing.

Histopathological and Biochemical Analysis

Macro- and microscopically, the histological analysis of the gastric mucosa were carried out.[38] The formalin-fixed stomach samples were put on a glass slide and divided into slices in the size of 4 µm. The Hematoxylin-Eosin (H and E) was used for staining the slices before being viewed under a Leica microscope.

To assess the functioning of the liver as well as kidneys of rats fed with synthetic substances and ibuprofen, the blood activity levels of AST and ALT, as well as the amounts of creatinine and urea, were measured.[39]

RESULTS

Synthesis of 5-amino (*N*-substituted carboxamide) quinoline derivatives

Figure 1 shows the synthetic plan as an illustration of the synthesis of the target compounds. The 5-amino(*N*-substituted carboxamide)quinoline derivatives were made in two stages via N-acylation reaction. The majority of acylation reactions are conducted in aprotic organic solvents like benzene, toluene, triethylamine, dichloromethane, pyridine, acetic acid, etc. The reaction is highly exothermic and must be carefully controlled by cooling the reaction mixture or performing the reaction mixture in very dilute solutions. In first step, trichloroacetyl chloride is reacted with +5°C solution of 5-aminoquinoline in non-nucleophilic tertiary base like triethylamine to give an intermediate 2,2,2-trichloro-*N*-quinolin-5-yl-acetamide. During this reaction, presence of triethylamine is crucial to neutralize the one equivalent of acid formed; otherwise, it will consume the amine and diminish the yield. Also, this organic base acts as catalyst in the reaction. In second step, 2,2,2-trichloro-*N*-quinolin-5-yl-acetamide is reacted with primary aliphatic or aromatic amine in presence of diazabicycloundecene to give 5-amino substituted quinoline carboxamide. The diazabicycloundecene is used in organic

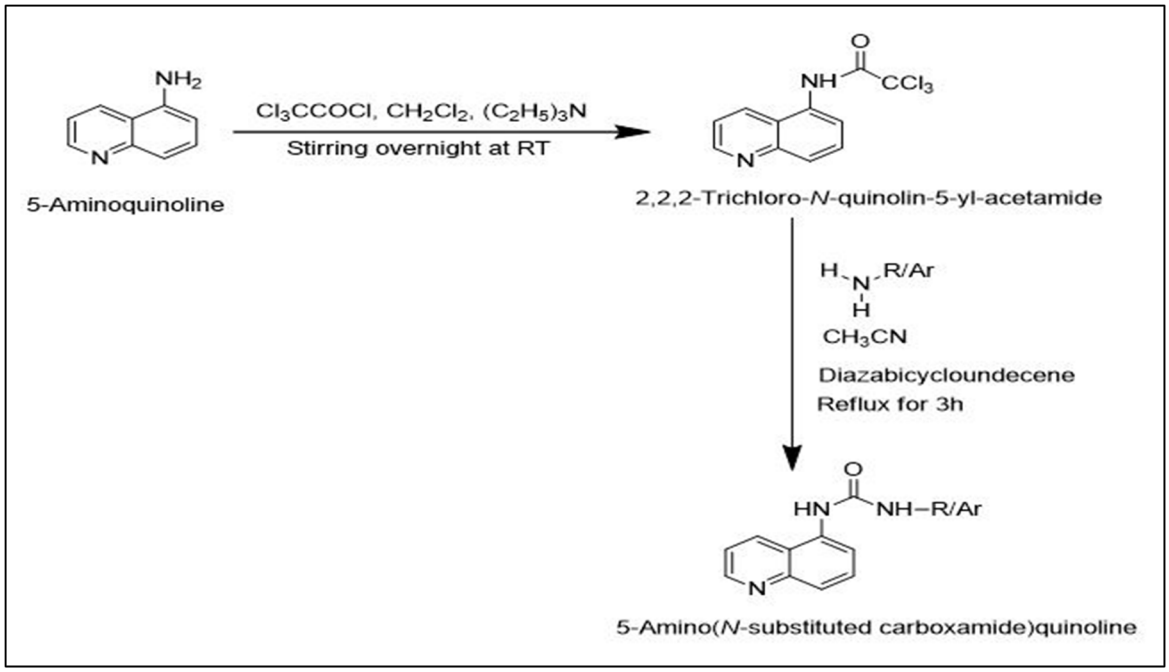

Figure 1: Scheme for the synthesis of 5-amino(*N*-substituted carboxamide)quinoline derivatives.

Table 1: Characterization of Synthesized Derivatives.

Compound Code	R/Ar	Molecular Formula	Molecular Weight (g)	% Practical yield	Melting point (°C)	R_f value
2o	2	$C_{19}H_{19}N_3O$	305.37	66.72%	287-289	0.57
2p	2	$C_{18}H_{17}N_3O$	291.35	68.54%	283-285	0.51
2q	2	$C_{17}H_{14}FN_3O$	295.11	71.56%	273-275	0.59
2r	2	$C_{16}H_{14}N_4O$	278.31	65.45%	303-305	0.52
2s	2	$C_{16}H_{12}BrN_3O$	342.19	75.58%	307-309	0.46
2t	2	$C_{15}H_{12}N_4O$	264.28	59.63%	299-301	0.58

synthesis as a catalyst, a complexing agent and non-nucleophilic base.

Six different derivatives (2o-2t), with yields varying from 59% to 76%, were synthesized. Uncorrected melting points were found. It was carried out using scientific melting point equipment. The solvent mixture selected for the thin layer chromatography was *n*-hexane: methanol (8:2). These descriptions are all listed in Table 1.

Spectral characterization of intermediate and synthesized derivatives[40]

Through the use of infrared, ^{1}H nuclear magnetic resonance and mass spectroscopy, the structures of the synthesized derivatives were verified. The expected region of an absorption band was seen in the IR spectra. According to ^{1}H nuclear magnetic resonance spectra at 500 MHz using DMSO solvent, aromatic and aliphatic groups' proton resonance signals were observed in the locations that were expected. The mass of the synthesized compounds was verified using their ESI spectra. The following are all of the mentioned spectrum descriptions of intermediate and synthetic derivatives.

Intermediate: 2,2,2-trichloro-*N*-quinolin-5-yl-acetamide

Molecular formula: C11H7Cl3N2O; Molecular weight: 289.55; % Practical yield: 80%;

Melting point: 313-315 °C; Rf value: 0.57;

IR (KBr): υ (cm-1) 3550 (N-H), 1700 (C=O), 1620 (C=N), 850 (C-Cl). 1H NMR: δ 3.56 (s, 1H, NH), 7.28 (t, 1H, Quinoline-H), 7.67-8.89 (d, 4H, Quinoline-H), 7.73 (t, 1H, Quinoline-H). ESI-MS: [M + H]+ m/z=290.9671.

Derivative 2o: 5-amino(*N*-[2,4,6-trimethylphenyl]carboxamide)quinoline

IR (KBr): υ (cm^{-1}) 3440 (N-H), 3020 (C-H), 1720 (C=O). ^{1}H NMR: δ 2.65 (s, 9H, CH_3), 3.56 (s, 1H, NH), 6.79 (s, 1H, CONH), 7.01 (s, 2H, Ar-H), 7.20-7.75 (t, 2H, Quinoline-H), 7.55-8.99 (d, 4H, Quinoline-H). ESI-MS: $[M + H]^+$ *m/z*=306.1391.

Derivative 2p: 5-amino(*N*-[2,4-dimethylphenyl]carboxamide)quinoline

IR (KBr): υ (cm^{-1}) 3300 (N-H), 3100 (C-H), 1640 (C=O). ^{1}H NMR: δ 2.63 (s, 6H, CH_3), 3.56 (s, 1H, NH), 6.79 (s, 1H, CONH), 6.81 (t, 1H, Ar-H), 6.83 (d, 1H, Ar-H), 7.20-7.75 (t, 2H, Quinoline-H), 7.64-9.01 (d, 4H, Quinoline-H), 7.77 (s, 1H, Ar-H). ESI-MS: $[M + H]^+$ *m/z*=279.1143.

Derivative 2q: 5-amino(*N*-[3-fluorobenzyl]carboxamide)quinoline

IR (KBr): υ (cm^{-1}) 3470 (N-H), 3100 (C-H), 1680 (C=O), 1400 (C-F). ^{1}H NMR: δ 3.56 (s, 1H, NH), 4.49 (s, 2H, CH_2), 6.79 (s, 1H, CONH), 7.05-7.11 (d, 2H, Ar-H), 7.19 (s, 1H, Ar-H), 7.28 (t, 1H, Quinoline-H), 7.35 (t, 1H, Ar-H), 7.65-8.99 (d, 4H, Quinoline-H), 7.73 (t, 1H, Quinoline-H). ESI-MS: $[M + H]^+$ *m/z*=296.1092.

Derivative 2r: 5-amino(*N*-[4-methylpyridin-2-yl]carboxamide)quinoline

IR (KBr): υ (cm^{-1}) 3350 (N-H), 3100 (C-H), 1690 (C=O). ^{1}H NMR: δ 2.12 (s, 3H, CH_3), 3.56 (s, 1H, NH), 6.79 (s, 1H, CONH), 6.95 (d, 1H, Pyridine-H), 7.20-7.75 (t, 2H, Quinoline-H), 7.64-9.01 (d, 4H, Quinoline-H), 7.68 (d, 1H, Pyridine-H), 8.24 (s, 1H, Pyridine-H). ESI-MS: $[M + H]^+$ *m/z*=279.1143.

Derivative 2s: 5-amino(*N*-[4-bromophenyl]carboxamide)quinoline

IR (KBr): υ (cm^{-1}) 3520 (N-H), 3200 (C-H), 1700 (C=O), 750 (C-Br). ^{1}H NMR: δ 3.56 (s, 1H, NH), 6.79 (s, 1H, CONH), 7.25 (t, 1H, Quinoline-H), 7.37 (d, 2H, Ar-H), 7.63-9.01 (d, 4H, Quinoline-H), 7.73 (t, 1H, Quinoline-H), 7.75 (d, 2H, Ar-H). ESI-MS: $[M + H]^+$ *m/z*=343.0143.

Derivative 2t: 5-amino(*N*-[pyridine-3-yl]carboxamide)quinoline

IR (KBr): υ (cm^{-1}) 3340 (N-H), 3150 (C-H), 1660 (C=O). ^{1}H NMR: δ 3.56 (s, 1H, NH), 6.79 (s, 1H, CONH), 7.28 (t, 1H, Quinoline-H), 7.31 (t, 1H, Pyridine-H), 7.47 (d, 1H, Pyridine-H), 7.65-9.01 (d, 4H, Quinoline-H), 7.73 (t, 1H, Quinoline-H), 8.40

(s, 1H, Pyridine-H), 8.41 (d, 1H, Pyridine-H). ESI-MS: $[M + H]^+$ *m/z*=265.3113.

Biological Evaluation

TRPV1 Inhibition by Antinociceptive Activity by Acetic acid-induced writhing test

This investigation was fulfilled by evaluating an antinociceptive impact of synthesized compounds upon inhibition of transient receptor potential vanilloid 1. The acetic acid-induced writhing test in rats' models has been employed for said activity. The writhing was induced by 0.6% acetic acid. Rat's abdominal writhes were used to measure the antinociceptive effects of the synthesized compounds, ibuprofen and control treatments. When comparing with the control value, the oral administration of the synthetic compounds 2o, 2p, 2q, 2r, 2s and 2t having the dose of 200 mg/kg and the intraperitoneal delivery of ibuprofen (100 mg/kg) resulted in a decrease in the number of writhes. Furthermore, Figure 2 showed that all compounds and standard ibuprofen considerably enhanced the percentage of inhibition relative to control (Table 2).

Ibuprofen with a dose of 100 mg/kg and the derivatives 2q, 2r and 2s (dose of 200 mg/kg each) showed the largest inhibitory effects

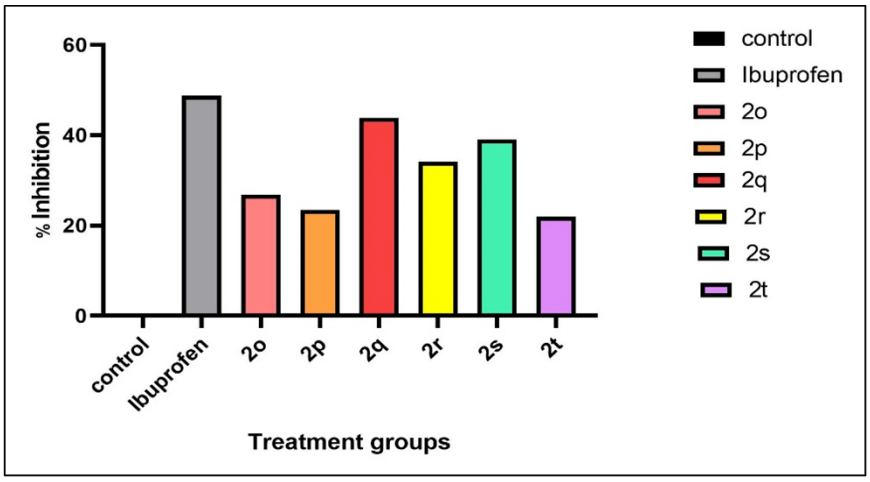

Figure 2: The percentage inhibition of acetic acid-induced writhing response in rats.

Table 2: Impact of synthesized derivatives (200 mg/kg), Ibuprofen (100 mg/kg) and control group on writhing induced by acetic acid in rats.

Treatment groups	Number of writhing	% Writhing	% Inhibition
Control	20.5±1.18	100	0
Standard Ibuprofen	10.5±0.43	51.21	48.78
2o	15.0±0.73	73.17	26.83
2p	15.7±0.95	76.58	23.41
2q	11.5±0.76	56.10	43.90
2r	13.5±0.76	65.85	34.15
2s	12.5±0.76	60.98	39.04
2t	16.0±1.15	78.05	21.95

Note: Each value represents the mean±SEM, N=6.

Table 3: Biochemical studies of rats' serum.

Treatment groups	AST (IU/L)	ALT (IU/L)	Creatinine (mg/dL)	Urea (mg/dL)
Control	125.75	39.34	0.29	23.18
2q	107.61	27.15	0.21	17.70
2r	115.43	35.47	0.25	21.53
2s	109.50	33.38	0.23	19.58
Ibuprofen	130.25	37.65	0.28	22.75

Reference Range;[41] ALT-13.5-56.0; AST- 50.0-150.0; Urea- 11.0-25.0; Creatinine-0.2-0.7.

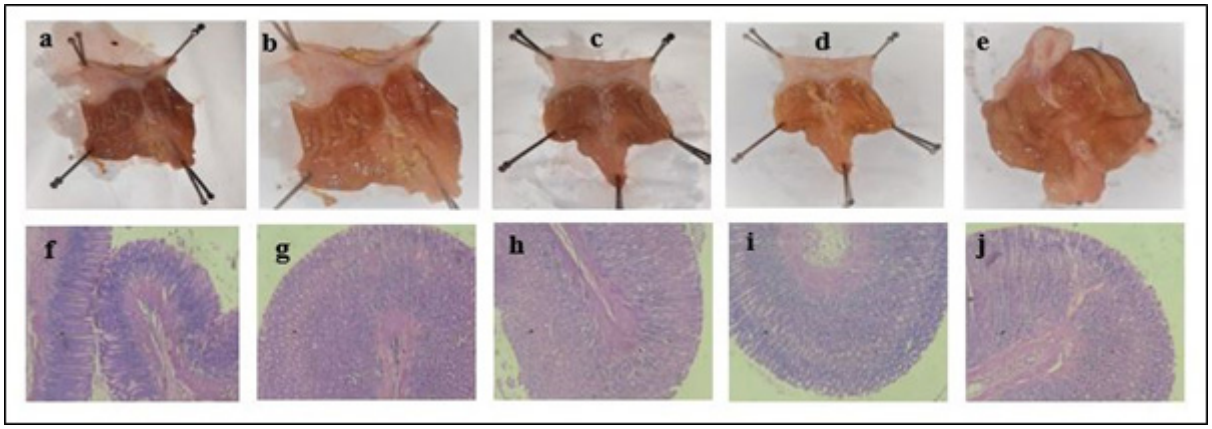

Figure 3: The macro- and microscopic appearance of stomach mucosa.

in animal groups when compared to controls, with 48.78%, 43.90%, 34.15% and 39.04% respectively.

Histopathological and Biochemical Analysis

Histopathological analysis

The goal of the study was to outline the compound's gastric safety aspects. The outcomes of the microscopic analysis confirmed the macroscopic modifications (Figure 3). Rats treated with 2q (Figure 3b, 3g), 2r (Figure 3c, 3h), 2s (Figure 3d, 3i), standard Ibuprofen (Figure 3e, 3j) and control (Figure 3a, 3f) showed no differences in stomach tissue's histology. The stomach mucosa's macroscopic features (3a, 3b, 3c, 3d and 3e) showed that the chemicals under investigation hardly ever caused gastrointestinal lesions. Hematoxylin-eosin-stained microphotographs of stomach tissue (3f, 3g, 3h, 3i and 3j) revealed that the examined derivatives had no impact on the stomach's normal cellular structure and did not cause ulcers.

Biochemical Analysis

The blood activity levels of AST along with ALT, together with the contents of creatinine along with urea, were checked in animals pretreatment with synthesized compounds 2q, 2r, 2s and standard Ibuprofen. This was performed for assessing the work of the liver and renal systems. Intraperitoneal injections of acetic acid did not significantly raise the serum AST as well as ALT level of activity or alter the amount of creatinine as well as urea when compared with the control (Table 3).

DISCUSSION

This work provided every parameter required to develop novel substituted quinoline compounds that target transient receptor potential vanilloid 1. The 5-amino (*N*-substituted carboxamide) quinoline derivatives (2o-2t) were synthesized and validated by FTIR, ^{1}H NMR and mass spectrum analyses, according to the findings of this study. In the predicted region, representative absorption bands were seen. The chemical shifts (δ) of the ^{1}H NMR were presented with units of parts per million (ppm). Hertz (Hz) was used for presenting the coupling constants (*J*) about internal Tetramethylsilane (TMS). Singlet (s), doublet (d), triplet (t) and quartet (q) were used as abbreviations to identify the splitting patterns. Important to keep in mind is the possibility of carefully altering chemical structures to produce new inhibitors that become more potent as well as effective over specific targets within biological conditions. Acetic acid-induced writhing in rats was used to target the antinociceptive activity of vanilloid 1, which has a transitory receptor potential. It is well known that the acetic acid model utilized an irritating chemical that results in necrosis of tissues within the cavity of the peritoneum. The main afferent nociceptors, which identify tissue damage, are typically activated or become more sensitive in response to this generated chemical irritant, which causes pain.[42] Research has demonstrated that the acetic acid writhing model can be utilized as a screening approach to assess potential antinociceptive drugs, hence it was chosen for the aforementioned investigation.[43] In comparison to the control value, oral treatment of the synthetic compounds 2o, 2p, 2q, 2r, 2s and 2t and intraperitoneal delivery of ibuprofen resulted in a considerable percentage reduction in the number of writhes. Additionally, the microscopic analysis of the stomach tissue conducted as part of the histological research reflected the macroscopic variations. The results of this investigation showed that neither control rats nor rats pretreated with 2q, 2r, or 2s or regular ibuprofen had any histological abnormalities in their stomach tissue. Given that the synthesized compounds function by blocking the TRPV1, it is suitable to perform a preliminary examination of the effect of pretreatment of these particular substances on the indications of damage to the kidneys, liver and mucosa of the stomach. Increases in serum alanine and aspartate transaminase activity could indicate severe liver damage or changes to the membrane permeability of hepatocytes. The markers ALT, as well as AST, are also useful for identifying liver necrosis or inflammation.[44] The kidneys physically filter urea as well as creatinine derived from blood. In blood, both factors are maintained. In renal diseases, the levels of both increases because kidneys are not able to efficiently remove them. As a result, both the levels of urea and creatinine are viewed as indications for

potential renal damage.[45] Different from ibuprofen, pretreatment with compounds 2q, 2r and 2s did not affect the ALT as well as AST activities and the urea as well as creatinine levels in comparison with control rats, according to the findings of the current investigation. This implies that at the studied levels, these novel derivatives are not harmful to the liver or kidneys.

CONCLUSION

A series of 5-amino(*N*-substituted carboxamide)quinoline derivatives (2o-2t) were synthesized via two steps. The structure of synthesized derivatives was verified by FT-IR, ^{1}H NMR and Mass spectroscopy. The findings presented here suggest that the 5-amino(*N*-substituted carboxamide)quinoline derivatives have antinociceptive activity. The derivatives inhibit transient receptor potential vanilloid 1 by using acetic acid-induced writhing in rats. Some derivatives are marginally as efficient as Ibuprofen and some are less efficient than Ibuprofen. Their undeniable benefit is that they do not harm the stomach mucosa or cause nephrotoxicity and hepatotoxicity as they do. Among all the compounds under study, compounds 2q, 2r and 2s reveal the most active derivatives. In light of this, it is possible to view the utilization of compounds 2q, 2r and 2s as a prospective therapeutic approach that may be helpful in the management of a variety of inflammatory illnesses. The outcomes of this investigation further demonstrate that the novel 5-amino(*N*-substituted carboxamide)quinoline derivatives are a promising starting point for future research into powerful and secure TRPV1 inhibitors.

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CONFLICT OF INTEREST

The authors declare that there is no Conflict of Interest.

ABBREVIATIONS

TRPV1: Transient Receptor Potential Vanilloid 1; **TLC:** Thin Layer Chromatography; **FT-IR:** Fourier Transform Infrared; **NMR:** Nuclear Magnetic Resonance; **DMSO:** Dimethyl sulfoxide; **TMS:** Tetramethylsilane; **ESI-MS:** Electron Spray Ionisation Mass Spectra; **AST:** Aspartate transaminase; **ALT:** Alanine transaminase.

SUMMARY

The synthesis, confirmation and assessment of a series of 5-amino(*N*-substituted carboxamide)quinoline derivatives (2o-2t) were done for their antinociceptive properties. These substances were used to target vanilloid 1, a transient receptor potential molecule. To target this receptor, rats were used in an acetic acid-induced writhing test. It was discovered that the compounds 2q, 2r and 2s performed better in this model. Additionally, histological and biochemical research was carried out. The named compounds 2q, 2r and 2s were shown to be as effective as the common medicine Ibuprofen in both studies.

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