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AN APPROACH TO SYNTHESIS OF TRAMADOL DRUG DERIVATIVES, CHARACTERIZATION PHARMACOKINETICS AND COMPARISON OF BIOLOGICAL ACTIVITIES

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Abstract

Derivatives of tramadol were synthesized by reflux action of tramadol with different amino acids and the structures of new derivatives were confirmed by physical characterization and spectral data; FTIR, NMR analysis. New compounds were screened against anti-inflammatory, analgesic and antioxidant activities. The physical properties like; color, physical state, melting points and the solubility of derivatives in various solvents were determined by respective techniques. All the synthesized products were tested for anti-inflammatory activity by carrageenan induced paw-edema in mice and the analgesic activity was evaluated by acetic acid-induced abdominal writhing in mice. The pharmacokinetic profile was predicted using Swiss ADME software. The antioxidant activity of esterified products was tested by DPPH free radical scavenging method. Esterified products of tramadol presented marked analgesic and antioxidant activity. The newly synthesized products also revealed significant anti-inflammatory activity.

Keywords: Analgesic, Anti-Inflammatory, Derivatization, FTIR, NMR, Physical Data, Tramadol

1. INTRODUCTION

Tramadol is a basic analgesic used for the treatment of moderate to severe pain [1-3]. It is well-tolerated and effective agent used for reduction of pain from trauma[4], labor[1], renal colic[5, 6], biliary colic, neuropathic pain[7] postoperative analgesia[8, 9], arthroscopic knee surgery[10], laparoscopic cholecystectomy[11], intracranial

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surgery[12], and is used for postoperative analgesia in cats[13] as well as in dogs that are undergoing enucleation[14]. Tramadol is prescribed progressively for the osteoarthritis treatment for the reason that, in contrast to NSAIDs, it does not cause renal problem, gastrointestinal bleeding or does not harm articular cartilage [15-17]. Tramadol/APAP moderates the cruelty of pain, phonophobia and photophobia supplementary to migraine headache [18] and is used effectively in the ailments of chronic, low back pain[19-22], fibromyalgia pain[23, 24] and cancer pain[25, 26] . It is not only used to alleviate the pain but also treat depression and anxiety [27, 28]. Far-now this has become the largest prescribed opioid worldwide [29, 30]. When administered orally, tramadol shows well absorption and rapid distribution in body, about 20% shows plasma protein binding, excretes mainly through kidneys, elimination half-life is about 6 hours [7, 31], 15-35 % of the parent drug is excreted out through kidneys unchanged [30, 32]. Tramadol evokes minor unwanted side-effects mainly euphoria, drug-dependence and tolerance [33] without inducing constipation and respiratory depression [29]. Tramadol produce post-operative pain relief comparable to pathidine, the analgesic effect of tramadol can be enhanced by combining with non-opioid analgesic [7, 34].

The purpose of this study is to synthesize new tramadol esters and evaluate their analgesic, anti-inflammatory, antioxidant and pharmacokinetic profile. The results of these experiments indicate that how the esters of tramadol change the tramadol efficacy in-vivo in formalin induced paw edema and acetic acid induced analgesia in experimental animals. This study also concentrates on antioxidant and Pharmacokinetics of newly synthesized tramadol esters when compared with tramadol. This approach in current study is distinctive to our science. The structures of the synthesized ester derivatives are given under **Figure 1.**

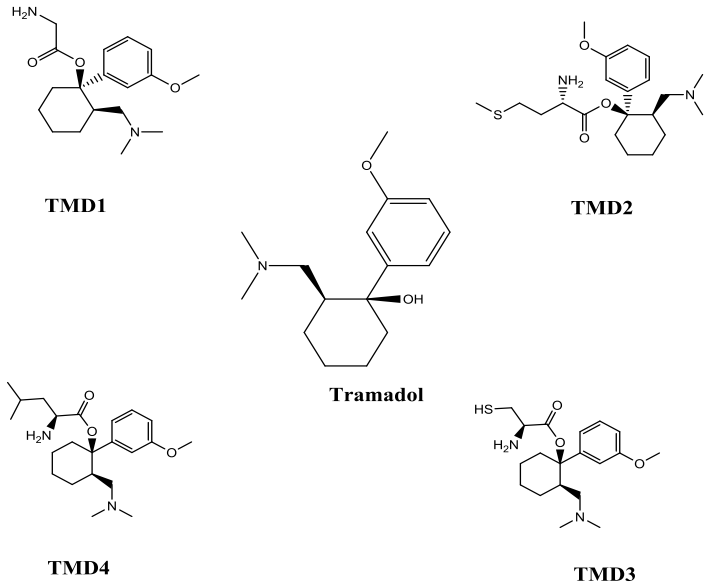

Figure 1: Structures of synthesized ester derivatives (TMD1-TMD4) of Tramadol

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2. MATERIAL AND METHODS

2.1. Chemicals and Reagents

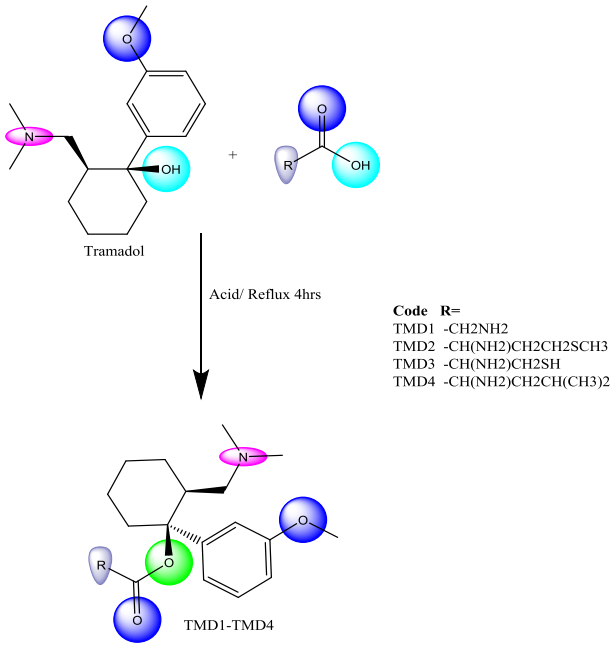
Tramadol (Supriya life science ltd), Culture media (oxioid), and all chemicals and solvents are of analytical grade and were purchased from sigma Aldrich. Solvents were purified by drying method.

2.2. Animals used

Albino mice from either sex weighing between 25-30g are being used. The mice were acclimatized at research laboratory of pharmacology in standard environmental conditions i.e.; 12 h dark: 12 h light cycles at 24±2 °C. The mice were treated as per standard guidance of National research council [35].

2.3. Synthesis of tramadol derivatives

Tramadol solution (10 ml, 0.1 M in methanol), amino acid solution (10ml, 0.1M in methanol) and 1 ml H_2SO_4 were added to 250ml 2-necked flask which is then refluxed for 4-5 hours and temperature was secured at 75°C. On completion, the color of solution turned yellow. The products were then neutralized using Na_2CO_3 that reacts with excess of sulfuric acid and concentrated to Na_2SO_4. Upon filtration, Na_2SO_4 remained on filter press as residue. The residues were washed with methanol and washing was also added to the neutralized filtrate. The contents are then dried to obtain esters of tramadol [36]. The formation of tramadol esters was confirmed by determining melting points (gallenkamp melting point apparatus) and FTIR peaks (Bruker FTIR).



Scheme1: Synthesis of Tramadol Derivatives (TMD1-TMD4)

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The physical characterization like color, physical state, melting point and chemical characters like IUPAC name, chemical formula, molecular weight, characteristic NMR and IR peaks data of tramadol as well as newly synthesized derivatives is described below

Tramadol, IUPAC Name; (1S,2S)-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol, M. P. 185-186°C. Molecular formula: $C_{16}H_{25}NO$ and molecular weight: 263.38 gm/mol. FT-IR v (cm^{-1}), 2952 (C-H), 1635 (C=N), 1603, 1476 (C=C), 1178 (C−N), ^{1}H NMR (DMSO, ppm) δ: 3.11 s (3H, CH_3), 2.12 s (3H, CH_3), 2.19 s (3H, CH_3), 2.05-2.06 d (2H, CH_2), 2.01-2.02 m (1H, CH), 1.50-1.51 m (2H, CH_2), 1.41-1.44 m (4H, CH_2), 1.78-1.79 m (2H, CH_2), 6.88-6.89 d (1H, CH), 7.10-7.11-d (1H, CH), 7.15 s (1H, CH), 7.22-7.23 t (1H, CH), 3.85 s (1H, OH), ^{13}C NMR (DMSO, ppm) δ: 65.8(C1), 39.3 (C2), 20.8 (C3), 25.1 (C4), 15.5 (C5), 31.4 (C6), 137.1 (C7), 104.8 (C8), 156.0 (C9), 109.3 (C10), 125.7 (C11), 115.6 (C12), 55.7 (C13), 45.6 (C14,15), 52.1 (C16).

TMD1, IUPAC Name: (1R, 2R)-2-((dimethylamino) methyl)-1-(3-methoxyphenyl)cyclohexyl 2-aminoacetate, Yield (72 %); Off white Powder M. P. 137°C. Molecular formula: $C_{18}H_{28}N_2O_3$ and molecular weight: 320.43 gm/mol. Elemental analysis (calculated) for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74, (found) C, 67.40; H, 8.84; N, 8.77, FT-IR v (cm^{-1}), 3008, 2940 (C-H), 1712, 1698 (C=N), 1603 (C=C), 1168 (C−N), ^{1}H NMR (DMSO, ppm) δ: 3.23 s (3H, CH_3), 2.16 s (3H, CH_3), 2.21 s (3H, CH_3), 3.51 s (2H, CH_2), 2.00-2.01 d (2H, CH_2), 1.91-1.93 m (1H, CH), 1.54-1.55 m (2H, CH_2), 1.38-1.39 m (4H, CH_2), 1.68-1.69 m (2H, CH_2), 6.61-6.62 d (1H, CH), 7.09-7.10 d (1H, CH), 7.18 s (1H, CH), 7.28-7.29 t (1H, CH), 1.48 s (2H, NH_2), ^{13}C NMR (DMSO, ppm) δ: 66.2 (C1), 41.3 (C2), 24.1 (C3), 27.6 (C4), 20.5 (C5), 33.4 (C6), 140.9 (C7), 108.0 (C8), 158.1 (C9), 111.3 (C10), 126.9 (C11), 117.0 (C12), 58.7 (C13), 44.6 (C14,15), 52.9 (C16), 160.2 (C17), 41.0 (C18).

TMD2, IUPAC Name; (S)-(1R, 2R)-2-((dimethylamino) methyl)-1-(3-methoxyphenyl)cyclohexyl 2-amino-4-(methylthio)butanoate, Yield (77 %); Yellow Liquid. Molecular formula: $C_{21}H_{34}N_2O_3S$ and molecular weight: 394.57 gm/mol. Elemental analysis (calculated) for $C_{21}H_{34}N_2O_3S$: C, 63.92; H, 8.69; N, 7.10; S, 8.13, (found) C, 63.90; H, 8.73; N, 7.12; S, 8.14, FT-IR v (cm^{-1}), 2924 (C-H), 1738 (C=O), 1596 (C=C), 1240 (C−N), 3374 (N-H), ^{1}H NMR (DMSO, ppm) δ: 3.25 s (3H, CH_3), 2.21 s (3H, CH_3), 2.15 s (3H, CH_3), 2.01 s (3H, CH_3), 1.95-1.96 d (2H, CH_2), 1.87-1.88 m (1H, CH), 1.47-1.48 m (2H, CH_2), 1.41-1.43 m (4H, CH_2), 1.63-1.64 m (2H, CH_2), 2.11-2.12 m (2H, CH_2), 2.61-2.62 t (2H, CH_2), 3.45 t (1H, CH), 6.65-6.66 d (1H, CH), 7.17-7.18 d (1H, CH), 7.23 s (1H, CH), 7.28-7.29 t (1H, CH), 5.01 s (2H, NH_2), ^{13}C NMR (DMSO, ppm) δ: 64.7 (C1), 40.3 (C2), 21.8 (C3), 26.2 (C4), 19.5 (C5), 33.2 (C6), 139.5 (C7), 106.7 (C8), 158.1 (C9), 114.3 (C10), 127.5 (C11), 119.2 (C12), 53.7 (C13), 42.6 (C14,15), 54.1 (C16), 161.5 (C17), 57.1 (C18), 35.1 (C19), 29.8 (C20), 10.7 (C21).

TMD3, IUPAC Name; (R)-(1R, 2R)-2-((dimethylamino) methyl)-1-(3-methoxyphenyl) cyclohexyl 2-amino-3-mercaptopropanoate, Yield (70 %); Liquid. Molecular formula: $C_{19}H_{30}N_2O_3S$ and molecular weight: 366.52 gm/mol. Elemental analysis (calculated) for $C_{19}H_{30}N_2O_3S$: C, 62.26; H, 8.25; N, 7.64; S, 8.75, (found) C, 62.22; H, 8.28; N, 7.67; S,

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8.71, FT-IR v (cm^{-1}), 2931 (C-H), 1739 (C=O), 1595, 1492 (C=C), 1243 (C−N), 3369 (N-H). ^{1}H NMR (DMSO, ppm) δ: 3.27 s (3H, CH_3), 2.12 s (3H, CH_3), 2.22 s (3H, CH_3), 3.58-3.59d (2H, CH_2), 2.08-2.09 d (2H, CH_2), 1.97-1.98 m (1H, CH), 1.57-1.58 m (2H, CH_2), 1.36-1.37 m (4H, CH_2), 1.60-1.61 m (2H, CH_2), 6.62-6.63 d (1H, CH), 7.15-7.16 d (1H, CH), 7.21 s (1H, CH), 7.27-7.28 t (1H, CH), 3.67-3.68 t (1H, CH), 4.98 s (2H, NH_2), 1.40 s (1H, SH), ^{13}C NMR (DMSO, ppm) δ: 65.3 (C1), 42.2 (C2), 22.7 (C3), 25.6 (C4), 19.5 (C5), 31.4 (C6), 138.9 (C7), 105.1 (C8), 154.2 (C9), 110.1 (C10), 128.5 (C11), 119.6 (C12), 58.6 (C13), 47.3 (C14,15), 52.5 (C16), 165.4 (C17), 53.7 (C18), 23.1 (C19).

TMD4, IUPAC Name: (S)-(1R, 2R)-2-((dimethylamino) methyl)-1-(3methoxyphenyl) cyclohexyl 2-amino-4-methylpentanoate, Yield (73 %); off white Powder, M. P. 187 °C. Molecular formula: $C_{22}H_{36}N_2O_3$ and molecular weight: 376.53 gm/mol. Elemental analysis (calculated) for $C_{22}H_{36}N_2O_3$: C, 70.18; H, 9.64; N, 7.44, (found) C, 70.25; H, 9.60; N, 7.48, FT-IR v (cm^{-1}), 3010, 2928 (C-H), 1738 (C=O), 1586, 1475 (C=C), 1174 (C−N), 3300 (N-H), ^{1}H NMR (DMSO, ppm) δ: 3.14 s (3H, CH_3), 2.26 s (3H, CH_3), 2.11 s (3H, CH_3), 0.71-0.72 d (3H, CH_3), 0.85-0.86 d (3H, CH_3), 2.00-2.01 d (2H, CH_2), 1.95-1.96 m (1H, CH), 1.78-1.79 m (2H, CH_2), 1.57-1.58 m (2H, CH_2), 1.45-1.46 m (4H, CH_2), 1.72-1.73 m (2H, CH_2), 6.60-6.61 d (1H, CH), 7.21-7.22 d (1H, CH), 7.26 s (1H, CH), 7.30-7.31 t (1H, CH), 3.43 m (1H, CH), 1.41-1.42 m (1H, CH), 5.10 s (2H, NH_2), ^{13}C NMR (DMSO, ppm) δ: 66.0 (C1), 39.8 (C2), 21.5 (C3), 25.4 (C4), 18.5 (C5), 31.9 (C6), 139.0 (C7), 109.7 (C8), 157.2 (C9), 112.3 (C10), 126.2 (C11), 114.5 (C12), 57.6 (C13), 43.9 (C14,15), 53.4 (C16), 164.7 (C17), 55.2 (C18), 43.1 (C19), 24.5 (C20), 21.1 (C21,22).

2.4. Analgesic activity by Acetic acid induced writhing's test

Acetic acid induced writhing's test was conducted following the methodology described by Eshola et al [37] with slight modification. Mice from either sex were randomly categorized in groups (n=3). Each group was administered orally with derivative of tramadol (40mg/kg body weight), tramadol (40mg/kg body weight) and distilled water. 60 minutes after treatment, each mouse was treated with 0.6 % acetic acid in normal saline (10ml/kg) IP. The numbers of writhing (contraction of the abdominal wall and extension of the hind limb) started 5 minutes after acetic acid treatment, shown by individual mouse were calculated for 10 minutes. The percent inhibition of writhing was evaluated by the formula:

$$\%\ inhibition = \frac{no\ of\ writhing\ (control) - no\ of\ writhing\ (test)}{no\ of\ writhing\ (conrol)} * 100$$

2.5. Anti-inflammatory activity by Carrageenan induced mice paw edema

Anti-inflammatory efficacy of tramadol esters at dose 40mg/kg was monitored by carrageenan induced paw edema in mice. Nine animals were categorized in 3 groups, each consisting of 3 animals. Control group was treated with distilled water only (2ml/kg/oral). Experimental group was treated with tramadol ester (40mg/kg/oral). Standard group was treated with tramadol (40mg/kg/oral). After 1 hour, a sub-plantar injection of 0.1ml suspension of carrageenan (1% w/v in normal saline) in the right hind

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paw of every animal is applied to induce the edema. The circumference of edematous paw was calculated using Vernier calipers at 0 min and at every 30 min intervals for 2 hours [35]. The formula used to calculate the %age inhibition is

$$\%\ inhibition = \frac{Vc - Vt}{Vc} * 100$$

Vt and *Vc* indicate the corresponding usual paw volume of treated and control animals.

2.6. Antioxidant activity by DPPH free radical scavenging method

The antioxidant activity of tramadol esters was evaluated by DPPH free radical scavenging, the change of optical density of 1-diphenyl-2-picrylhydrazyl (DPPH) is observed. 0.5mg/ml solution of standard drug (ascorbic acid) and all test samples in methanol was diluted with 2ml DPPH stock solution (7.89 g/100ml in methanol) and kept at room temperature in complete dark for 30 minutes, followed by measurement of absorbance at 517 nm [38] [39]. The percentage of DPPH radical is calculated as;

$$\%\ inhibition = \frac{Absorbance\ of\ standard - Absorbance\ of\ product)}{Absorbance\ of\ standard} * 100$$

2.7. ADME Pharmacokinetic Studies

To select an agent as a drug, there is a high influence of physical and molecular properties of that agent. In order to confirm the potential of the new derivatives as therapeutic target ligands, the Swiss ADME web server (http://www.swissadme.ch) is being employed to scrutinize the molecular characteristics of the synthesized derivatives. The pharmacokinetic parameters like water solubility, lipophilicity and aabsorption of each drug were added as a smile format. The topolological polar surface area was used to compute the percentage of absorption (%ABS) of new derivatives.

$$\%\ ABS = 109 - (0.345\ TPSA)$$

3. RESULTS AND DISCUSSIONS

The analgesic potential of tramadol and synthesized derivatives calculated by acetic acid induced analgesia in mice is tabulated in table 1.

Table 1: Acetic acid induced analgesic activity of tramadol and its derivatives

Derivative Dose:(40 mg/kg)	No of writhing	% inhibition
Control (10ml/kg)	99 ± 0.577	---
TMD 1	6.67 ± 0.33	93.33
TMD 2	66.33 ± 2.19	33.67
TMD 3	12 ± 0.58	88
TMD 4	11.67 ± 0.88	88.33
TMD	16.33 ± 0.88	83.67

Values are expressed as means ± SEM (n=3).

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The experimental animals which were treated with TMD 1 at dose 40 mg/kg exhibited highly significant reduction in the numbers of writhing with inhibition of 93.33%, whereas the treatments with TMD 3 showed significant reduction in acetic acid induced writhing in experimental animals with percent inhibition 0f 88% when compared with standard drug tramadol (% inhibition: 83.67) at the same dose (table 1). The maximum analgesic effect was shown by tramadol derivative TMD1 that shows it is a potent analgesic derivative of tramadol in this study. The anti-inflammatory efficacy analyzed by carrageenan induced paw edema in experimental animals is listed in table 2.

Table 2: Carrageenan induced paw edema anti-inflammatory activity of tramadol and its derivatives

Derivative Dose (40 mg/kg)	Increase in paw size (% inhibition)				
	$T_{0\ min}$ (mm)	$T_{30\ min}$ (mm)	$T_{60\ min}$ (mm)	$T_{90\ min}$ (mm)	$T_{120\ min}$ (mm)
Control (2ml/kg)	3.06 ± 0.001	3.9 ± 0.003	4.02 ± 0.003	4.35 ± 0.003	4.52 ± 0.003
TMD 1	2.61 ± 0.001 (19.62)	2.99 ± 0.003 (23.5)	2.88 ± 0.003 (28.23)	2.96 ± 0.003 (31.93)	2.75 ± 0.003 (39.05)
TMD 2	2 ± 0.0002 (34.62)	3±0.003 (23.01)	2.7 ± 0.003 (32.71)	2.55 ± 0.003 (45.35)	2.48 ± 0.003 (45.03)
TMD 3	2.58 ± 0.0002 (15.66)	2.98±0.003 (23.73)	2.98 ± 0.003 (25.89)	2.2 ± 0.003 (49.53)	2.41 ± 0.003 (46.71)
TMD 4	2.31 ± 0.003 (24.60)	2.96 ± 0.003 (24.24)	2.26 ± 0.003 (43.81)	2.47 ± 0.003 (43.33)	2.47 ± 0.003 (45.38)
TMD	2.14 ± 0.001 (29.98)	2.7±0.003 (30.75)	2.58 ± 0.003 (35.7)	2.54 ± 0.001 (41.63)	2.22 ± 0.003 (50.92)

Values are expressed as means ± SEM (n=3). Values in parenthesis exhibit the percent inhibition of edema produced.

Tramadol derivatives significantly reduced the carrageenan induced paw edema in experimental animals at assessment times. When treated with 40 mg/kg dose; at 0 minute, TMD 2, showed significant ant-inflammatory effects with % inhibition 0f 34.62 %, when compared to standard drug tramadol at the same dose (% inhibition 29.98 %), while TMD 1 and TMD 4 also showed marked inhibition i.e. 19.62% and 24.6% respectively. At 60 minutes, TMD 2 showed significant reduction in paw edema i.e. 32.71% whereas TMD 4 showed highly significant anti-inflammatory activity i.e. 43.81% as compared to tramadol i.e. 35.7%. At 90 minute interval, TMD 2 and TMD 4 produced significant anti-inflammatory effect with % inhibition of 45.35 %, and 43.33 % respectively while highly significant effect was shown by TMD 3 i.e., 49.53% when compared with tramadol that showed 41.63 % inhibition at the same interval. After 2 hours of dosing, significant results were shown by TMD2, TMD 3 and TMD 4 i.e., 45.03 %, 46.71 % and 45.38 % respectively. The maximum anti-inflammatory effect at the same dose and time interval was shown by TMD i.e, 50.92 % (table 2).

The results of anti-oxidant activity of tramadol and its derivatives against free radical DPPH scavenging method are tabulated in table 3.

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Table 3: DPPH free radical scavenging antioxidant activity of tramadol and its derivatives

Derivative (Dose=0.5mg/ml)	Antioxidant activity (% inhibition)
TMD 1	65.83 ± 0.44
TMD 2	78.67±0.09
TMD 3	97.87±0.07
TMD 4	62.33 ±0.03
TMD	59.53 ± 0.09
Control/Blank	4.500
Standard	98.1

Values are expressed as means ± SEM (n=3).

In antioxidant activity consideration, all the derivatives TMD1, TMD 2, TMD 3 and TMD 4 showed excellent potential i.e., 65.83 %, 78.67 %, 97.87 % and 62.33 % respectively which is comparable to TMD (59.53%) and standard drug ascorbic acid (98.1%) (table 3).

The findings of ADME pharmacokinetics are tabulated in Table 4.

Table 4: Predicted ADME properties of Tramadol and its derivatives

Derivative	(TPSA)	GI absorption	BBB permeability	Lipinski violation	Bioavailability	% ABS
TMD 1	64.79	high	Yes	0	0.55	86.65
TMD 2	90.09	high	No	0	0.55	77.92
TMD 3	103.59	high	No	0	0.55	73.29
TMD 4	64.79	high	Yes	0	0.55	86.65
TMD	32.7	high	Yes	0	0.55	97.72

*TPSA (Topological Polar Surface Area), *GI = gastrointestinal, *BBB = blood brain barrier, *%ABS = percentage absorption.

The absorption and release profile of an oral medication is influenced by the formulation and the physicochemical properties of the drug as well as the anatomy and the physiology of the gastrointestinal track. During drug development the bioavailability (B.A) of a new drug is assessed in the early clinical studies. Even an alteration in the anatomy and/ or physiology of the gastrointestinal tract can associate many disease conditions [40].

4. CONCLUSIONS

The current research was executed to synthesize the ester base derivatives of tramadol drug. The spectral analysis validated the synthetic protocols of the newel synthesized derivatives. An analysis of the in-vivo results indicate that the newly synthesized derivatives of tramadol presented analgesic, anti-inflammatory and antioxidant actions through related mechanisms. The results are comparable to parent drug as well as reference material. Some of the derivatives showed enhanced biological activities to parent drug. Because of their improved analgesic, anti-inflammatory and antioxidant potential, some of the derivatives can be used as lead compounds for treatments of underlined diseased by overcoming the drug resistance and GIT disturbance.

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Nevertheless further researches are required to synthesize new derivatives and validate their structures to use in in clinical trials and further for the treatment of various ailments.

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