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(54) **Title:** NOVEL SULFONANILIDE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME AND PROCESS THEREOF

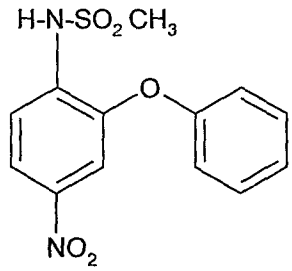
(57) **Abstract:** Novel sulfonanilide derivatives, preferably derivatives of N-(4-Nitro-2-phenoxy-phenyl)methane-sulfonamide, and their pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof are provided. Also provided are process of preparation of such novel derivatives, pharmaceutical composition comprising the same and method of using such compositions for the prophylaxis, amelioration and/or treatment of inflammation and/or pain, and other associated disorders which comprises administering to a subject in need thereof an effective amount of such composition. The novel derivatives have improved solubility, preferably aqueous solubility, and/or improved bioavailability and/or reduced adverse effects associated with therapy.

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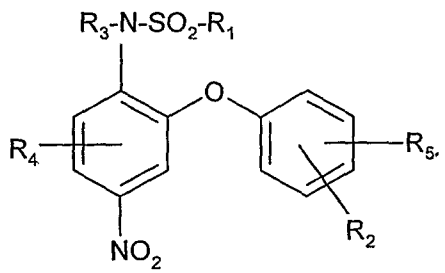
NOVEL SULFONANILIDE DERIVATIVES, PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME AND PROCESS THEREOF

FIELD OF THE INVENTION

The present invention relates to novel sulfonanilide derivatives and their pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof. Particularly the present invention relates to novel derivatives having the general formula as shown in Formula-II, which are the derivatives of N-(4-Nitro-2-phenoxy-phenyl)methane-sulfonamide (also known as nimesulide) having the formula as shown in Formula-I, and their pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof. The novel derivatives have improved solubility, preferably aqueous solubility, and/or improved bioavailability with reduced adverse effects associated with the therapy. Further, this invention relates to process of preparation of such novel derivatives, pharmaceutical composition comprising the same and method of using such compositions for the prophylaxis, amelioration and/or treatment of inflammation and/or pain, and other associated disorders which comprises administering to a subject in need thereof an effective amount of such composition.



Formula-I



Formula-II

Wherein:

R_1 = an alkyl group 1-3 carbon atomic number, cycloalkyl group 3-6 atomic number, a phenyl group, or a substituted phenyl group, more particularly acetylaminophenyl group, or an aromatic heterocyclic group preferably having a 5-membered or 6-membered ring comprising a N and/or S and/or O,

R_2 = a phenyl group, a halophenyl group, an amino group, a lower alkyl amino group, an allyl group, a vinyl group, an amino acid group, a lower N-substituted carboxy alkyl, or a lower N,N-disubstituted carboxy alkyl group, or an aromatic heterocyclic group preferably having a 5-membered or 6-membered ring comprising a N and/or S and/or O,

R_3 = -H,

$-CH_2COOH$ or its water soluble base addition salts,

$-CH_2-(CH_2)_n-COOH$, where n = 1-4 or their physiologically acceptable organic or inorganic base addition salts,

$-CO-CHX-NH_2$ (X is alkyl, a substituted alkyl, an aryl, a substituted aryl, a heterocyclic compound, or a physiologically acceptable organic or inorganic acid salt), or

- an aromatic heterocyclic group preferably having a 5-membered or 6-membered ring comprising a N and/or S and/or O, and

R_4 = hydrogen, halogen, lower alkyl, an aryl or a substituted aryl, or a heterocyclic group.

R_5 = hydroxyl or an alkoxy group.

The novel derivatives of the present invention possess improved solubility, preferably aqueous solubility, and/or improved bioavailability with reduced adverse effects associated with the therapy and can be easily be formulated into desired pharmaceutical compositions which can be administered orally, parenterally, or by any route of administration.

BACKGROUND OF THE INVENTION

Non-steroidal anti-inflammatory drugs, which suppress inflammation and/or pain in a manner similar to steroids, but without the side effects of steroids, and commonly referred to by acronym NSAIDs, have been extensively used clinically in treatment of various inflammations (such as osteoarthritis, inflammation of respiratory tract), back pain, sciatica, sprains, strains, dental pain, migraine, rheumatism, post-operative pain, period pain (dysmenorrhoea) and heavy periods (menorrhagia), pain from kidney stones (renal colic),

particularly useful in the inflammatory forms of arthritis (e.g. rheumatoid arthritis) and, sometimes, in more severe forms of osteoarthritis, besides its use also as an antipyretic. The role of prostaglandins in the induction of inflammation and the enzyme for its synthesis, cyclooxygenase, was known since 1970s. Prostanglandins are neutral chemicals which are involved in body inflammation by inhibiting the body's production of certain chemical messengers. However, certain prostaglandins are also important in protecting the stomach lining from the corrosive effects of stomach acid as well as playing a role in maintaining the natural healthy conditions of the stomach lining. These prostaglandins are produced by an enzyme called COX-1. The cyclooxygenase exists in two-isoforms viz. cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). The selective inhibitor of COX-2 will suppress prostaglandin synthesis at the sites of inflammation but it won't interfere with the activity of COX-1, in tissues like GI tract. Therefore, NSAIDs, which belong to COX-2 inhibitors, are commonly used in clinical context. Among them, sulfonanilide such as nimesulide, would inhibit preferentially COX-2 more than COX-1 and is better tolerated by the gastrointestinal tract compared to other conventional NSAIDs. However, in recent years, there have been a number of reports worldwide of adverse side effects associated with NSAID therapy. Another negative property of nimesulide from its formulation perspective is its poor solubility in water (approximately 0.01 mg/ml). Due to the poor solubility of nimesulide, it becomes very difficult to manufacture some galenic compositions such as drinkable and injectable solution and some oral preparations. Further, the poor solubility leads to poor bioavailability of nimesulide in vivo. Furthermore, since nimesulide has an acidic proton in its chemical structure, it can form a salt with alkali metals or organic bases. The water soluble form in particular the sodium salt, impose a relatively alkaline pH or is far from the physiological values, so it is poorly tolerated.

PCT Publication Nos. WO 91/17774 and WO94/02177 disclose nimesulide complex with cyclodextrins that improve the aqueous solubility of nimesulide upto 5 times the solubility of nimesulide. PCT Publication No. WO94/15932 describes thiophene and furan derivatives which selectively inhibit COX-2. PCT Publication No. WO 95/15316 describes pyrazolyl sulfonamide derivative which selectively inhibit COX-2. However, in certain circumstances, prodrugs of anti-inflammatory compounds are advantageous, especially where the prodrug have increased water solubility or delayed onset of action. Compounds which selectively inhibit COX-2 have been described. Nimesulide, having the Formula-I as herein described, is

known from US Patent Nos. 3840597 and European Patent No. 1604976. US Patent No. 4866091 relates to alkali sulfonamide derivative and acceptable salts thereof which have anti-inflammatory and analgesic activities and their pharmaceutical compositions. US Patent No. 5344991 describes cyclopentenes which selectively inhibit COX-2. US Patent No. 5393790 describes spiro compounds which selectively inhibit COX-2.

None of the prior arts describe sulfonanilide derivatives particularly derivatives of nimesulide which have a substantially improved aqueous solubility and/or bioavailability, and which can easily be formulated into desired pharmaceutical compositions that are effective but safe. Hence, there still exists a need for developing novel sulfonanilide derivatives with such aforementioned desirable properties, which the present invention provides.

SUMMARY OF THE INVENTION

It is an objective of the present invention to provide novel sulfonanilide derivatives and their pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof.

It is an objective of the present invention to provide novel derivatives having the general Formula-II as stated herein, of N-(4-Nitro-2-phenoxy-phenyl)methane-sulfonamide having the Formula-I as stated herein, and their pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof.

It is another objective of the present invention to provide pharmaceutically acceptable water soluble salt of novel sulfonanilide derivative.

It is also another objective of the present invention to provide process of preparation of such novel derivatives having the general Formula-II as stated herein.

It is yet another objective of the present invention to provide pharmaceutical compositions comprising such novel derivatives having the general Formula-II as stated herein and process of preparation of such compositions.

It is a further objective of the present invention to provide a method of using such novel

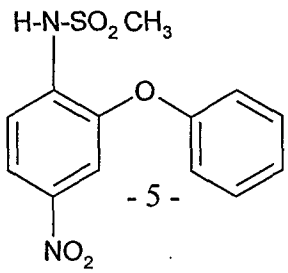
derivatives or pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof; or pharmaceutical compositions comprising such novel derivatives or pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof, which comprises administering to a subject in need thereof an effective amount of such novel derivatives or composition thereof.

The novel derivatives or pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof, of the present invention possess improved solubility, preferably aqueous solubility, and/or improved bioavailability and/or reduced adverse effects associated with therapy. The novel derivatives are preferably capable of being administered for showing activity for longer periods of time, and are highly effective especially for the treatment of inflammation and/or pain or other associated disorders.

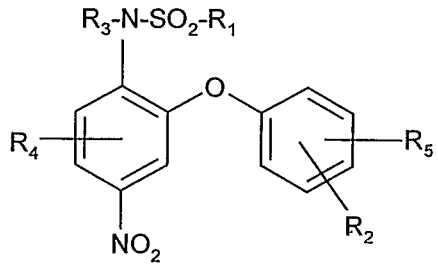
The novel derivatives or pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof, of the present invention can easily be formulated into desired pharmaceutical compositions which can be administered orally, parenterally, or by any route of administration.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel sulfonanilide derivatives and their pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof. In a preferred embodiment, the present invention provides novel derivatives having the general Formula-II as stated herein, of N-(4-Nitro-2-phenoxy-phenyl) methane-sulfonamide having the Formula-I as stated herein and their pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof.



Formula-I



Formula-II

Wherein:

R_1 = an alkyl group 1-3 carbon atomic number, cycloalkyl group 3-6 atomic number, a phenyl group, or a substituted phenyl group, more particularly acetylaminophenyl group, or an aromatic heterocyclic group preferably having a 5-membered or 6-membered ring comprising a N and/or S and/or O,

R_2 = a phenyl group, a halophenyl group, an amino group, a lower alkyl amino group, an allyl group, a vinyl group, an amino acid group, a lower N-substituted carboxy alkyl, or a lower N,N-disubstituted carboxy alkyl group, or an aromatic heterocyclic group preferably having a 5-membered or 6-membered ring comprising a N and/or S and/or O,

R_3 = -H,

$-CH_2COOH$ or its water soluble base addition salts,

$-CH_2-(CH_2)_n-COOH$, where n = 1-4 or their physiologically acceptable organic or inorganic base addition salts,

$-CO-CHX-NH_2$ (X is alkyl, a substituted alkyl, an aryl, a substituted aryl, a heterocyclic compound, or a physiologically acceptable organic or inorganic acid salt), or

- an aromatic heterocyclic group preferably having a 5-membered or 6-membered ring comprising a N and/or S and/or O, and

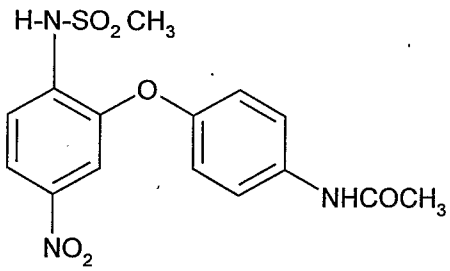
R_4 = hydrogen, halogen, lower alkyl, an aryl or a substituted aryl, or a heterocyclic group.

R_5 = hydroxyl or an alkoxy group.

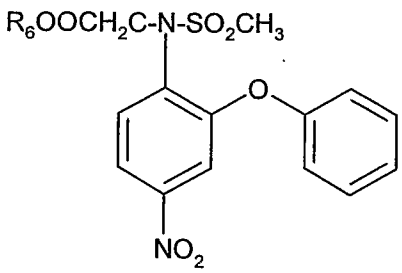
The novel derivatives have improved anti-inflammatory and/or analgesic and/or antipyretic and/or antiallergic activity and are highly useful for the management such as prophylaxis, amelioration and/or treatment of inflammatory diseases or pain or other associated disorders with reduced side effects associated with such active agents such as gastro-intestinal disorders and the like. Furthermore, the novel derivatives of the present invention are capable of being administered for longer time periods, have excellent safety profile and improved water solubility.

The inventors of the present invention using intellectual expertise and careful experimentation have designed and synthesized novel sulfonanilide derivatives particularly derivatives of nimesulide or salts thereof which have a substantially improved aqueous solubility and/or bioavailability, and which can easily be formulated into desired safe and effective compositions.

In an embodiment, the present invention provides novel derivatives of nimesulide represented by Formulas III, IV, V, VI and VII respectively.

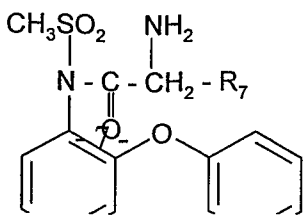


Formula-III



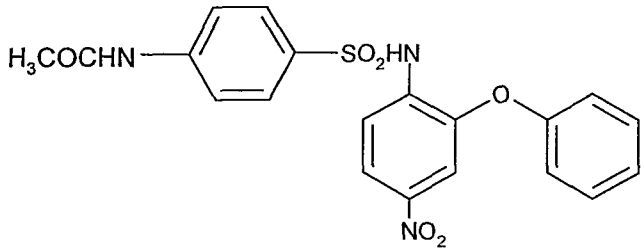
Formula-IV

Wherein R_6 is H or a physiologically acceptable organic or inorganic cation.

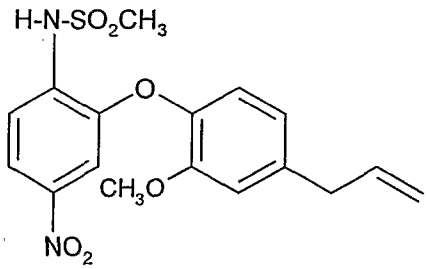


Formula-V

Wherein R_7 is alkyl, substituted alkyl, aryl, or substituted aryl.



Formula-VI

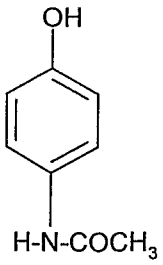


Formula-VII

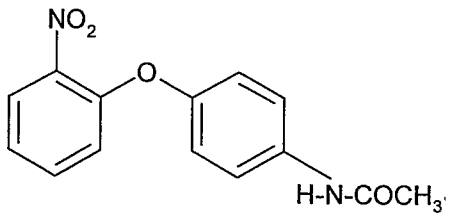
According to the further embodiment of the present invention the method of preparation of a product of Formula-III comprises the following steps:

i) A compound of the Formula-VIII, namely 4-hydroxyacetanilide, when reacted with 2-halonitrobenzene ('halo' being selected from the group consisting of fluoro, bromo, choloro and iodo), in the presence of a base, selected from the group comprising of alkali metal hydroxides and/or mild bases, for example, alkali metal carbonates and/or sodium and/or potassium methoxide, sodium and/or potassium ethoxide, sodium and/or potassium hydride, sodium and/or potassium t-butoxide and the like in the absence or presence of the solvent such as dipolar aprotic solvents, for example dimethylformamide and the like, and/or selected from the group consisting of aliphatic cyclic ethereal solvents, for instance

dioxane and the like, and/or from the group consisting of non polar water immiscible solvents, for example toluene and the like, yielded a compound represented by Formula-IX.



Formula-VIII



Formula-IX

ii) The compound of Formula-IX, wherein – NO_2 (nitro) group is reduced to – NH_2 (amino) group occurs by using conventional reducing agents for example, catalytic reduction using palladium or platinum in a suitable alcoholic solvent at a temperature ranging between 0°C to reflux temperature of the solvent used and also by any other reducing methods known in the art, for instance, use of metal ions in acidic and/or basic reaction conditions so as to yield required amino derivative in a suitable physiologically acceptable organic solvent such as an alcoholic solvent. Preferably, said alcoholic solvent used is ethanol.

iii) The above stated amino form is sulphonated with a suitable sulphonating agent selected from but not limited to a group comprising CH_3SO_2Z and/or $(CH_3SO_2)_2O$, wherein Z is selected from the group comprising of halogen atom, preferably chloro, in the presence of a pharmaceutically acceptable organic solvent, preferably selected from aprotic solvents having low polarity, ethereal solvents and/or dipolar aprotic solvents, advantageously a halogenated solvent e.g. dichloromethane, and in the presence or absence of pharmaceutically acceptable organic or inorganic base or by means of a suitable acid acceptor. In an

embodiment, the acid acceptor is triethylamine.

iv) The intermediate so obtained as per the above method was then subjected to nitrating mixture for the introduction of nitro group at the required position by means of nitration methods known in the art, selected from a group comprising chloroform/nitric acid, or acetic acid/nitric acid or sulphuric acid/nitric acid and the like, but not limited to the aforesaid group, so as to get the compound represented by Formula-III.

According to yet another embodiment of the present invention, the compound of Formula-IV is prepared in the following manner: reacting N-(4-Nitro-2-phenoxy phenyl) methane sulfonamide, i.e. nimesulide, of Formula-I as herein described as starting material with Q-alkyl-$COOR_5$, wherein Q belongs to the class of halo atoms, more specifically, bromo, and alkyl refers to lower alkyl, more preferably from C-1 to C-6 atomic number, typically methylene, and R_5 is H and/or lower alkyl selected from but not limited to a group comprising methyl, ethyl, propyl, t-butyl, lower aromatic and the like, in the presence or absence of a suitable physiologically acceptable organic base, for instance, as described herein above and in a suitable organic solvent, for instance dipolar aprotic solvent and also as described herein above so as to furnish the desired compound of Formula-IV.

According to yet another embodiment of the present invention, the compound of Formula-V is prepared in the following manner: reacting N-(4-Nitro-2-phenoxy phenyl) methane sulfonamide of Formula-I or its alkali metal salt, more preferably sodium or potassium, as starting material with Z-OC-CHX-NH_2 (with protected NH_2 group), wherein X is defined above and Z belongs to the class of halo atoms, more preferably chlorine atom, in the absence or presence of an organic aminic base, more preferably for instance, triethylamine, in a suitable organic solvent, for instance halogenated solvents preferably dichloromethane, and also as described herein above so as to furnish the desired compound represented by Formula-V.

According to yet another embodiment of the present invention, the compound of Formula-VI is prepared in the following manner:

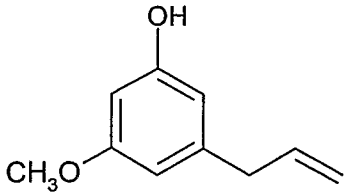
i) reacting 2-phenoxy aniline, an easily available intermediate of nimesulide, with

suitable sulphonating agent, for instance, $ArSO_2Z$, wherein Ar is selected from but not limited to the group comprising aryl or substituted aryl preferably acetyl amino phenyl, and Z belongs to the class of halogen atoms preferably chlorine atom, in the presence of an organic aminic base for instance triethylamine and the like in a suitable organic solvent for instance aprotic polar solvent, preferably tetrahydrofuran to give sulfonanilide.

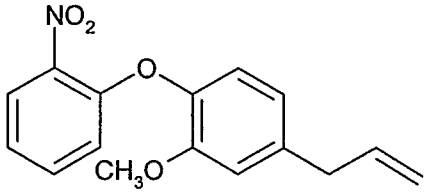
ii) subjecting the said sulfonanilide to nitrating mixture for the introduction of nitrate group at the desired position by means of nitration methods known in the art, selected from a group comprising chloroform/nitric acid or in acetic acid/nitric acid or sulphuric acid/nitric acid and the like, so as to get the compound represented by Formula-VI.

According to yet another embodiment of the present invention, the compound of Formula-VII is prepared in the following manner:

i) A compound of the Formula-X, namely 4-allyl-2-methoxyphenol, when reacted with 2-halonitrobenzene ('halo' being selected from the group consisting of fluoro, bromo, choloro and iodo), in the presence of a base, selected from the group comprising of alkali metal hydroxides and/or mild bases, for example, alkali metal carbonates and/or sodium and/or potassium methoxide, sodium and/or potassium ethoxide, sodium and/or potassium hydride, sodium and/or potassium t-butoxide and the like in the absence or presence of the solvent such as dipolar aprotic solvents, for example dimethylformamide and the like, and/or selected from the group consisting of aliphatic cyclic ethereal solvents, for instance dioxane and the like, and/or from the group consisting of non polar water immiscible solvents, for example toluene and the like, yielded a compound represented by Formula-XI.



Formula-X



Formula-XI

ii) The compound of Formula-XI, wherein – NO_2 (nitro) group is reduced to – NH_2 (amino) group occurs by using conventional reducing agents for example, metal ions in acidic and/or basic reaction conditions at a temperature ranging between 0°C to reflux temperature of the solvent used so as to yield required amino derivative in a suitable physiologically acceptable organic solvent such as a less polar solvent selected from but not limited to a group comprising dichloromethane or toluene or the like or mixtures thereof.

iii) The above stated amino form is sulphonated with a suitable sulphonating agent selected from but not limited to a group comprising CH_3SO_2Z and/or $(CH_3SO_2)_2O$, wherein Z is selected from the group comprising of halogen atom, preferably chloro, in the presence of a pharmaceutically acceptable organic solvent, preferably selected from aprotic solvents having low polarity, ethereal solvents and/or dipolar aprotic solvents, advantageously a halogenated solvent e.g. dichloromethane, and in the presence or absence of pharmaceutically acceptable organic or inorganic base or by means of a suitable acid acceptor. In an embodiment, the acid acceptor is triethylamine.

iv) The intermediate so obtained as per the above method was then subjected to nitrating mixture for the introduction of nitro group at the required position by means of nitration methods known in the art, for instance in chloroform/nitric acid, or acetic acid/nitric acid or sulphuric acid/nitric acid and the like, but not limited to the aforesaid group, so as to get the compound represented by Formula-VII.

According to the present invention, the mixture of novel derivatives of the present invention can be in the form of an associate or a complex or inclusion compounds with the pharmaceutically acceptable excipients. For example, a mixture of the novel derivatives and povidone can be in the form of an associate of the novel derivatives with povidone, a mixture of novel derivatives and phospholipid can be in the form of a complex, and a mixture of the derivatives with cyclodextrin can be in the form of an

inclusion of the novel derivatives in cyclodextrin.

Pharmacokinetic Study: Different pharmacokinetic studies were performed on four nimesulide (NIM) derivatives as indicated hereinafter. PAR-NMS chemically known as 4-Nitro-2-[(4`-Acetylamino)-phenoxy]-methanesulfonyl aniline (Formula III); ACT-NMS chemically known as N-(4-Nitro-2-phenoxyphenyl) methanesulfonyl aniline acetic acid (Formula IV); Acetyl-NMS chemically known as N-(4-Nitro-2-phenoxyphenyl) acetylsulfanilyl aniline (Formula VI) and EUG-NMS chemically known as N-(4-Nitro-2-(4-allyl-2-methoxyphenoxy) phenyl)-methanesulfonamide (Formula VII).

A pharmacokinetic study has been carried out to study the analgesic effect of nimesulide derivatives, namely compounds of Formula- III and Formula-IV (wherein R_5 is H) as stated herein against acetic acid-induced writhing in mice. Swiss albino mice (18-22 g) of either sex were selected for the study comprising 5 to 6 animals in each group for the period of 6 hours with sampling intervals of 1, 3 and 6 hours. A dose of 2.5 mg/kg, p.o. of nimesulide and molar equivalent dose of nimesulide derivative was administered through oral route.

Acetic acid-induced writhing assay was conducted by carrying out abdominal constriction test in mice. Abdominal constrictions (development of tension in abdominal muscles, elongation of the body and hind limb, arching of back) after 3 minutes of injection of acetic acid (1% v/v, 10 mL kg^{-1}, i.p.) were recorded in mice as a response to nociceptive stimuli for 20 minutes. Nimesulide (2.5 mg/kg p.o.) or its derivatives described herein as compounds of Formula-III also referred to herein as PAR-NMS and Formula-IV (wherein R_5 is H) also referred to herein as ACT-NMS (dose equivalent to nimesulide) were administered 1h, 3h and 6h before acetic acid-challenge in mice. The number of writhes was expressed as mean ± S.E.M. and analyzed by one-way ANOVA followed by Student-Newman-Keuls multiple-range test. $P<0.05$ was considered statistically significant. The time course of nimesulide (2.5 mg/kg, p.o.) and its derivatives PAR-NMS and ACT-NMS at molar equivalent dose was assessed in acetic acid-induced writhing in mice. Both PAR-NMS and ACT-NMS showed significant analgesic effect (reduction in number of writhes) when administered 3h before acetic acid challenge as compared to control group. The effect was comparable to nimesulide.

Further, both PAR-NMS and ACT-NMS administered 1 h before acetic acid challenge demonstrated analgesic effect as compared to control group, which was not comparable to time-matched nimesulide group and after 3 hours comparable to nimesulide. However, a 6h pre-treatment with PAR-NMS but not ACT-NMS showed a significant analgesic effect as compared to control group, which was statistically higher than nimesulide group. The result of the study is presented in Table 1.

Table 1: Analgesic effect of nimesulide and its derivatives (ACT-NMS and PAR-NMS) against acetic-acid induced writhing in mice (n = 5-6)

S. No.	Group No.	Sampling Interval	Treatment (mg/kg, p.o.)	No. of writhes (mean ± SEM)
1.	1	----	Control	36.87 ± 2.30
2.	2	1 h	Nimesulide (2.5)	16.5 ± 1.60
		1 h	ACT-NMS (2.97)	27.16 ± 1.64*
		1 h	PAR-NMS (2.96)	28.0 ± 2.27*
3.	3	3 h	Nimesulide (2.5)	16.50 ± 1.21*
		3 h	ACT-NMS (2.97)	16.64 ± 1.31*
		3 h	PAR-NMS (2.96)	15.07 ± 1.54*
4.	4	6 h	Nimesulide (2.5)	27.29 ± 3.90*
		6 h	ACT-NMS (2.97)	30.38 ± 2.49
		6 h	PAR-NMS (2.96)	13.54 ± 1.26*[a]

ACT-NMS & PAR-NMS doses are molar equivalents to nimesulide 2.5 mg/kg.

* $P<0.05$ as compared to control group.

[a] $P<0.05$ as compared to nimesulide-treated group.

Another pharmacokinetic study has been carried out to study the analgesic effect of nimesulide derivatives, namely compounds of Formula- VI and Formula-VII as stated herein against acetic acid-induced writhing in mice. Swiss albino mice (20-22 g) of either sex were selected for the study comprising 5 to 6 animals in each group. A dose of 4.0 mg/kg, p.o. of nimesulide and molar equivalent dose of nimesulide derivative was administered through oral route, before acetic acid-challenge in mice. All the drugs were suspended in 1% v/v Tween80-water and administered in a dose volume of 10ml/kg control animals received 1% v/v Tween80-water in a dose volume of 10ml/kg body weight.

Acetic acid-induced writhing assay was conducted by carrying out abdominal constriction test in mice. Abdominal constrictions (development of tension in abdominal muscles, elongation of the body and hind limb, arching of back) after 3 minutes of injection of acetic acid (1% v/v, 10 ml kg^{-1}, i.p.) were recorded in mice as a response to nociceptive stimuli for 15 minutes, 3 minutes after the administration of acetic acid. Nimesulide (4.0 mg/kg p.o.) or its derivatives described herein as compounds of Formula-VI also referred to herein as Acetyl-NMS and Formula-VII also referred to herein as EUG-NMS (dose equivalent to nimesulide) were administered 0.5h before acetic acid-challenge in mice. The number of writhes was expressed as mean ± S.E.M. and analyzed by one-way ANOVA followed by Student-Newman-Keuls multiple-range test. $P<0.05$ was considered statistically significant. The effect of nimesulide (4.0 mg/kg, p.o.) and its derivatives Acetyl-NMS and EUG-NMS at molar equivalent dose was assessed in acetic acid-induced writhing in mice. Both Acetyl-NMS and EUG-NMS showed significant analgesic effect (reduction in number of writhes) against acetic acid–induced writhing in mice as compared to control group. The result of the study is presented in Table 2. It was concluded that Acetyl-NMS (5.52 mg/kg) and EUG-NMS (4.90 mg/kg) produced a superior or at least comparable analgesic activity when compared to nimesulide-treated group.

Table 2: Analgesic effect of nimesulide and its derivatives (Acetyl-NMS and EUG-NMS) against acetic-acid induced writhing in mice (n = 5-6)

Treatment (mg/kg, p.o.)	**No. of writhes (mean ± SEM)**
Control (1% w/v Tween80-water, 10ml/kg)	53.77 ± 2.14
Nimesulide (4.0)	35.0 ± 2.23*
Acetyl-NMS (5.52)	33.75 ± 2.46[a]
EUG-NMS (4.90)	29.16 ± 1.76[b]

Acetyl-NMS and EUG-NMS doses are molar equivalents to nimesulide 4.0 mg/kg.

* $P<0.05$ as compared to control group.

[a] $P<0.05$, [b] $P<0.05$ as compared to nimesulide-treated group.

Yet another pharmacokinetic study has been carried out to study the antipyretic effect of nimesulide derivatives, namely compounds of Formula- III and Formula-VI as stated

herein against lipopolysaccharide (LPS)-induced febrile response in rats. Wistar rats (180-220 g) of either sex were selected for the study comprising 3 animals in each group. A dose of 5 mg/kg, p.o. of nimesulide and molar equivalent dose of nimesulide derivative was administered through peroral route. The basal rectal temperature was measured by inserting the rectal probe, a plastic coated thermocouple attached to a thermometer up to 2.2 cm in the rectum of the rat (Tele-thermometer, dual channel, Electronic manufacturing corporation, Chennai). LPS dissolved in saline was injected intraperitoneally in a dose of 100 µg/rat (Paul et al., 1999) and the rectal temperature was recorded at 1, 2, 3, and 4h. All other drugs were suspended in 0.5% w/v CMC containing Tween 80 (0.1%v/v) and administered per orally in a constant volume of 10 ml/kg body weight, 30 minutes before administration of LPS. Rats injected with LPS displayed a biphasic response. A significant increase in rectal temperature (hyperthermia) was observed at 1 hr of its injection (pretreatment value: 35.6 ± 0.2 °C; 1hr post treatment value: 37.0 ± 0.3 °C) as compared to the control group (pretreatment value: 35.4 ± 0.05 °C; 1h post treatment value: 35.2 ± 0.04 °C). However, after 2, 3, and 4h of LPS-challenge rats exhibited hypothermia (decrease in temperature) (Figure-1). The observation is in concordance to earlier reports in the literature which demonstrated that systemic administration of lipopolysaccaharide (LPS) to rodents, produced biphasic effect in body temperature with initial hyperthermia followed by prolonged hypothermia (Paul et al., 1999). Oral administration of nimesulide (5 mg/kg, po), PAR-NMS (5.9 mg/kg, po) and Acetyl-NMS (6.9 mg/kg, po) prevented hyperthermia induced by lipopolysaccharide in rats at 1hour. The change in rectal temperature following different treatments is represented in Figure-2. It was concluded that PAR-NMS treatment enhanced the hypothermic response of LPS compared to nimesulide showing significant antipyretic activity.

Still another pharmacokinetic study has been carried out to study the gastrotolerability of nimesulide derivatives, namely compounds of Formula-VI and Formula-VII as stated herein against nimesulide in rats. Wistar rats (140-170 g) of either sex were selected for the study comprising 5 animals in each group. A dose of 50 mg/kg (ulcerogenic dose), p.o. of nimesulide and molar equivalent dose of nimesulide derivative was administered through per oral route. The animals are randomly divided into different groups and receive one of the following treatments for 15 days: Nimesulide (50mg/kg), Acetyl-NMS

(69.0 mg/kg), EUG-NMS (61.0 mg/kg) and vehicle (10 mg/kg, p.o.). The drugs were suspended in [0.5% CMC containing Tween80 (1% w/v)] and administered in a constant dose volume of 10ml/kg body weight. On day 16, the overnight fasted animals were euthanized. The abdomen was cut open to isolate stomach. The stomach was excised from greater curvature and rinsed with saline. The ulceration in the antral region was quantified as per the method of Singh et al., 2005 (Singh VP et al., 2005, Effect of licofelone against NSAIDs-induced gastrointestinal ulceration and inflammation, 43:247-253). Spot ulcers were assigned a score of 1, and lesions were scored according to their length (a score of 5 for lesions with length between 1 and 3 mm; a score of 10 for lesions greater than 3 mm). The sum of total scores was used for comparison. The rats treated with vehicle did not show any inflammation or ulceration of the stomach. Three rats out of five (One each on day 4, 5, and 7) died during treatment with Nimesulide (50.0 mg/kg, po X 15d). Those found dead or otherwise sacrificed terminally were subjected to macroscopic examination of stomach. Slight inflammation (red coloration) and ulcers were observed in the stomach of the rats treated with Nimesulide. Similarly, two rats out of five (one each on day 8, and 9) treated with EUG-NMS (61.0 mg/kg, po X 15d) were found dead. The rats which died during the treatment or sacrificed terminally showed presence of inflammation in stomach. However, no ulcer formation was observed in the stomach following treatment with EUG-NMS. No death was observed in the rats treated with Acetyl-NMS (69 mg/kg X 15d). All of the animals treated with Acetyl-NMS were sacrificed at the end of treatment examine the stomach morphology. No signs of inflammation or ulceration were found in the stomach and the stomach was morphologically normal as for control rats. It was concluded that the treatment with EUG-NMS showed a better or at least comparable gastrotolerability as nimesulide and treatment with Acetyl-NMS, for 15 days at a dose equivalent to ulcer producing dose of nimesulide, did not produce any death, showed no signs of inflammation or ulceration in the stomach and was thus most gastrotolerable amongst Nimesulide and its derivatives tested herein.

Another pharmacokinetic study has been carried out to study the gastrotolerability effects of nimesulide derivatives, namely compounds of Formula-III and Formula-IV as stated herein against nimesulide in rats. Wistar rats (140-170 g) of either sex were selected for the study comprising 5 animals in each group. A dose of 50 mg/kg p.o. of

nimesulide and molar equivalent dose of nimesulide derivative was administered through per oral route. The animals are randomly divided into different groups and receive one of the following treatments for 15 days: Nimesulide (50mg/kg), ACT-NMS (59.35 mg/kg), PAR-NMS (59.19 mg/kg) and vehicle (10 mg/kg). The drugs were suspended in Tween80-water (1% w/v) and administered in a constant dose volume of 10ml/kg body weight. On day 16, the overnight fasted animals were euthanized. The abdomen was cut open to isolate stomach. The stomach was excised from greater curvature and rinsed with saline. The ulceration in the antral region was quantified as per the method of Singh et al., 2005 (Singh VP et al., 2005. Effect of licofelone against NSAIDs-induced gastrointestinal ulceration and inflammation. 43:247-253). Spot ulcers were assigned a score of 1, and lesions were scored according to their length (a score of 5 for lesions with length between 1 and 3mm; a score of 10 for lesions greater than 3mm). The sum of total scores was used for comparison. Data presented as mean ± S.E.M. was analyzed by one-way ANOVA followed by post hoc Dunnett's test. $P<0.05$ was considered statistically significant. It was observed that Nimesulide (50mg/kg, po X 15d), ACT-NMS (59.35 mg/kg, po X 15d) or PAR-NMS (59.19 mg/kg, po X 15d) treatment to rats produced ulceration in stomach as compared to Tween 80-water treated animals. Further, it was observed that the ulcer score of stomach of rats treated with ACT-NMS or PAR-NMS was statistically lower than nimesulide group (Figure-3). It was thus concluded that ACT-NMS or PAR-NMS showed better gastrotolerability as compared to Nimesulide tested herein.

From the abovesaid pharmacokinetic studies performed on various derivatives of Nimesulide, it was concluded that out of all the derivatives which were synthesized and studied, Acetyl-NMS possesses the best anti-inflammatory and/or antipyretic activity and is more gastrotolerable as compared to Nimesulide. Further, it was concluded that ACT-NMS and PAR-NMS are safer compounds compared to Nimesulide since they produced negligible side effects (inflammation and ulcer) as compared to Nimesulide. Moreover, the anti-inflammatory activity of ACT-NMS and PAR-NMS is initiated after a certain time period, thus the said derivatives can be given as an admixture with Nimesulide wherein the anti-inflammatory activity may be sustained for longer duration of time. Furthermore, it was also concluded that EUG-NMS is a safer and a gastrotolerable compound as it does not cause any ulceration in the stomach as compared to Nimesulide.

In another embodiment, the present invention provides pharmaceutically acceptable water soluble salt of novel sulfonanilide derivative. In a further embodiment, a pharmaceutically acceptable salt of compound according to Formula-II, as used herein, refers to a salt formed with a pharmaceutically acceptable organic or inorganic cation and/or base, for example, a salt with alkali metal or an alkaline earth metal, selected from but not limited to a group comprising sodium, potassium, calcium and magnesium and for example a salt with primary, secondary, tertiary and quaternary amines, selected form but not limited to a group comprising mono-, di- and tri-methylamine, propylamine 2-hydroxypropylamide, diethylamine, lysine, arginine, ornithine, N-methylglucamine, triethanolamine, cetylpyridinium, benzalkonium, choline and the like or mixtures thereof. In another embodiment, the present invention provides pharmaceutical compositions comprising such novel derivatives having the general Formula-II as stated herein and process of preparation of such compositions. The novel derivatives of the present invention can be easily be formulated into desired pharmaceutical compositions which can be administered orally, parenterally, topically, transdermally, rectally or by any route of administration. The novel derivatives of the present invention possess improved solubility, preferably aqueous solubility, and/or improved bioavailability with reduced adverse effects associated with therapy. The novel derivatives are preferably capable of being administered for longer periods of time, and are highly effective especially for the treatment of inflammation and/or pain or other associated disorders.

In a further embodiment of the present invention, the dosage form also contains pharmaceutically acceptable excipients known to the art such as but not limited to diluents, disintegrants, binders, preservatives, stabilizers, solubilizers, surfactants, buffers, salts for regulating the osmotic pressure, emulsifiers sweeteners, dyes, flavourings and the like when required for peculiar treatments.

According to the present invention, the novel derivatives represented by compound corresponding to Formula-II can be administered alone or in the form of a pharmaceutical composition. The pharmaceutical composition of the present invention can be administered orally, parenterally or topically and the dosage form can be tablet, capsule, drops, injection, suppository, patch, ointment and the other formulations for oral administration, injection or topical application. In an embodiment, the

pharmaceutical composition may additionally contain other pharmacologically active ingredient(s) whose concurrent administration may be useful.

In a further embodiment of the present invention, the pharmaceutical composition can be prepared by well known methods in the art, e.g. by mixing the compound of Formula-II with one or more pharmaceutically acceptable excipient(s) optionally with other active ingredient(s). The solid dosage forms can be produced by known methods such as direct compression, granulation, compaction, extrusion, molding, or the like using conventional excipients such as fillers, binders, disintegrants, glidants, lubricants, or the like, or mixtures thereof. For semi-solid or liquid preparations, in additional to a solid excipients, liquid and/or semi-solid excipients known to the art are used. For the preparation of an injectable composition such as an intra-venous or intra-muscular injection, the novel derivatives are treated with pharmaceutical excipients such as solvents, buffers, and the like, known to a person skilled in art.

In an embodiment, the amount of the novel derivatives of the present invention to be incorporated into the pharmaceutical composition of the present invention can vary over a wide range depending on known factors such as, for example, the disorder to be treated, the severity of the disorder, the patient's body weight, the dosage form, the chosen route of administration and the number of administration per day. However, selection of optimum amount is simple and routine for a person skilled in the art. Typically, the amount of product of Formula-II in the pharmaceutical composition of the present invention will range from approximately 5 mg to about 800 mg. In an embodiment, the daily posology comprises the administration of an effective amount of derivative represented by the Formula-II preferably at a dose and/or frequency lesser or at least comparative to the dose of nimesulide.

In another embodiment, the present invention provides a method of using such novel derivatives or pharmaceutical compositions comprising such novel derivatives which comprise administering to a patient in need thereof an effective amount of such novel derivatives or composition thereof. Preferably the novel derivatives and the compositions comprising the novel derivatives of the present invention are useful in the treatment of inflammation and/or pain associated with, for example, osteoarthritis, respiratory tract inflammation, postoperative pain, inflammation of the ear, nose and throat, headache,

toothache, post-traumatic pain, fever and the like, or other associated disorders.

The following examples are only intended to further illustrate different embodiments of the invention, and are therefore not deemed to restrict the scope of the invention in any way.

Example 1: Preparation of 4-Nitro-2-[(4`-Acetyl amino)-phenoxy]-methanesulfonyl aniline [Formula-III]

i) Preparation of 2-(4-Acetylamino-phenoxy)-nitrobenzene (A): 1 g of p-acetylaminophenol was added to 30 ml of dioxane suspension containing 0.36g of 60% sodium hydride at room temperature over a 15 minutes period and its mixture was stirred at the same temperature for about 1 hour. The mixture was heated to 50°C and agitated for 3.5 hours and then cooled to room temperature. 10 ml of dioxane containing 1.13 g of 2-Fluoro nitrobenzene was added dropwise and the mixture was stirred at room temperature overnight. The dioxane was evaporated followed by extraction of residue with chloroform and then the chloroform layer was washed with water and brine, and then dried over anhydrous sodium sulphate. The solvent was evaporated to give 1.5 g of the crude product (A).

ii) Preparation of 2-(4`Acetylamino-phenoxy) aniline (B): 50 ml of ethanol solution containing 3.7 g of (A) and 0.2 g of 5% palladium on carbon was stirred at room temperature under a hydrogen pressure of 3.0 kg for catalytic reduction. The catalyst was removed by filtration and the filtrate was evaporated to give 2.9 g of (B).

iii) Preparation of 2-(4`Acetylamino-phenoxy)-methanesulfonyl aniline (C): 1.2 g of (B), 0.75 g of triethylamine and dichloromethane were charged together in a 100 ml assembly. The reaction mixture was cooled to 0°C and 0.625 g of methanesulfonyl chloride was charged dropwise for 4 hours at 0–5°C. After completion of the addition, the mixture was stirred at room temperature for 2 hours. After stirring, the reaction mixture was quenched with water and the organic layer was extracted with 2N sodium hydroxide (NaOH) solution. The basic layer obtained was acidified with concentrated hydrochloric acid (HCl) and the reaction mixture was cooled to give 1.4g of (C).

iv) Preparation of 4-Nitro-2-[(4`-Acetylamino)-phenoxy]-methane sulfonyl aniline [Formula-III]: 1.4 g of (C) was dissolved in 30 ml of chloroform. The reaction

mixture was heated to 50°C and nitric acid was charged dropwise for about 1 hour. The reaction mixture was heated for 3 hours at 50°C. The reaction mixture was cooled to room temperature and then diluted with chloroform. The reaction mixture was washed with water, the organic layer was passed through sodium sulphate, and the solvent was recovered completely. The product was crystallized in ethanol and filtered to give 1.2 g of 4-Nitro-2-[(4`-Acetylamino)-phenoxy]-methanesulfonyl aniline [Formula-III] having the following NMR data:

^{1}H-NMR (DMSO-d6): δ2.063 (s, 3H), 3.012 (s, 3H), 6.9-7.8 (m, Ar-H, 7H), 9.0 (s, 1H), 9.44 (s, 1H)

Example 2: Preparation of N-(4-Nitro-2-phenoxy-phenyl) methanesulfonyl aniline acetic acid [Formula-IV]:

i) Preparation of N-(4-Nitro-2-phenoxy-phenyl)methanesulfonyl aniline acetic acid t-butyl ester (D): (10 mmol) of Nimesulide was charged into 10 ml of dimethyl acetamide and stirred for 10 minutes at room temperature. (12 mmol) of sodium hydride was charged into the above solution and the solution was agitated for further 20 minutes at room temperature. (10 mmol) of t-butyl chloroacetate was charged into the above solution and the reaction mass was stirred at 50-60°C for 15 hours. After stirring the extract, the product in ethyl acetate on recovery gave (8 mmol) of compound (D).

ii) Preparation of N-(4-Nitro-2-phenoxy-phenyl) methanesulfonyl aniline acetic acid [Formula-IV]: (8 mmol) of compound (D) was charged into 10 ml of formic acid. The reaction mixture was agitated for 2-3 hours at 50°C and then the reaction mixture was put in water. The reaction mixture was then extracted with ethyl acetate. The product was purified by column chromatography by eluting with a mixture of ethyl acetate and hexane to give N-(4-Nito-2-phenoxy-phenyl) methanesulfonyl aniline acetic acid [Formula-IV] as a off-white solid, having the following NMR data:

^{1}H-NMR ($CDCl_3$-): δ 3.1 (s, 3H), 4.5 (s, 2H), 7.0-7.9 (m, Ar-H- 8H)

Example 3: Preparation of N-(4-Nitro-2-phenoxyphenyl) acetylsulfanilyl aniline [Formula-VI]:

i) Preparation of N-(2-phenoxyphenyl) acetylsulfanilyl aniline (E): 7 g of 2-phenoxy aniline, 5.67 g of triethylamine and tetrahydrofuron were charged together in a 250 ml assembly. The reaction mixture was cooled to 0°C and 10.6 g of N-acetyl sulfaninyl chloride dissolved in tetrahydrofuran was charged dropwise for 3 hours at 0-5°C after completion of the addition, the mixture was stirred at 0-5°C for 1 hour, and at room temperature for whole night. After stirring the solvent was recovered completely and dichloromethane was charged, reaction mixture was quenched with water and the organic layer was extracted with 2N Sodium hydroxide solution. The basic layer was acidified with concentrated hydrochloric acid (HCl) and the reaction mixture was cooled to give 6 g of (E).

ii) Preparation of N-(4-Nitro-2-phenoxyphenyl)acetylsulfanilyl aniline[Formula-VI]: 5 g of (E) and 100 ml of acetic acid was charged in 250 ml assembly. The reaction mixture was heated to 70°C and 10 ml of acetic anhydride was charged. After charging acetic anhydride, Nitric acid was charged dropwise for about 1.5 hours. The reaction mixture was heated for 3 hours at 70°C. The reaction mixture was cooled to room temperature. After cooling, reaction mixture was quenched with water and filtered to give the crude product. The product was purified by column chromatography by eluting with a mixture of ethyl acetate and hexane to give N-(4-Nitro-2-phenoxyphenyl)acetylsulfanilyl aniline[Formula-VI] as a yellow solid, having the following NMR data

^{1}H-NMR ($CDCl_3$): δ 2.22 (s, 3H), 6.85 – 7.93 (m, 14H)

Example 4: Preparation of N-(4-Nitro-2-[(4-allyl-2-methoxyphenoxy) phenyl)-methanesulfonamide [Formula-VII]

i) Preparation of 2-(4-allyl-2-methoxyphenoxy)-nitrobenzene (F): 1 g of 4-allyl-2-methoxyphenol was added to 100 ml of dioxane suspension containing 1.8g of 60% sodium hydride at room temperature for about 1 hour. The mixture was heated to 50°C and agitated for 3.5 hours and then cooled to room temperature. 20 ml of dioxane containing 5.1 g of 2-Fluoro nitrobenzene was added dropwise and the mixture was stirred at room temperature overnight. The dioxane was evaporated followed by extraction of residue with chloroform and then the chloroform layer was washed with water and brine, and then dried over anhydrous sodium sulphate. The solvent was evaporated to give 11.8 g of the crude product (F).

ii) Preparation of 2-(4-allyl-2-methoxyphenoxy) aniline (G): 6.2 g of iron powder was added to 40 ml of water containing 0.865 ml of concentrated hydrochloric acid (HCl). The reaction mixture was heated to 80°C and 5 g of (F) was charged portion wise in 1.5 hours. The reaction mixture was again heated to 90°C for 2.5 hours. The reaction mixture was cooled to room temperature and basified with 2N-sodium hydroxide (NaOH) solution. 100 ml of toluene was charged to the reaction mixture, heated to 70°C and filtered while hot. The two layers were separated and the organic layer was passed through sodium sulphate and the solvent was recovered completely to give 4.0 g of (G).

iii) Preparation of N-(2-(4-allyl-2-methoxyphenoxy) phenyl)-methanesulfonamide (H): 3.0 g of (G), 1.77 g of triethylamine and dichloromethane were charged together in a 100 ml assembly. The reaction mixture was cooled to 0°C and 1.614 g of methanesulfonyl chloride was charged dropwise for 4 hours at 0–5°C. After completion of the addition, the mixture was stirred at room temperature for 2 hours. After stirring, the reaction mixture was quenched with water and the organic layer was extracted with 2N NaOH solution. The basic layer obtained was acidified with concentrated HCl and the reaction mixture was cooled to give 3.2g of (H).

iv) Preparation of N-(4-Nitro-2-[(4-allyl-2-methoxyphenoxy) phenyl)-methanesulfonamide [Formula-VII]: 5.0 g of (H) and 100 ml of acetic acid was charged in a 250 ml assembly. The reaction mixture was heated to 70°C and 10 ml of acetic anhydride was charged. After charging with acetic anhydride, 0.835 ml of nitric acid was charged for about 1 hour. The reaction mixture was heated for 3 hours at 70°C. The reaction mixture was cooled to room temperature. After cooling, the reaction mixture was quenched with water and filtered to give the crude product. The product was purified by column chromatography by eluting with a mixture of ethyl acetate and hexane to give N-(4-Nitro-2-[(4-allyl-2-methoxyphenoxy) phenyl)-methanesulfonamide [Formula-VII] (yield 65%) having the following NMR data:

^{1}H-NMR ($CDCl_3$): δ3.12 (s, 3H), 3.42 (d, 2H), 3.76 (s, 3H), 5.13-5.18 (m, 2H), 5.94-6.05 (m, 1H), 6.84-6.86 (m, Ar-2H), 7.07-7.09 (d, Ar-1H), 7.54-7.55 (d, Ar-2H), 7.59 (s, HH-1H), 7.73-7.25 (d, Ar-1H), 7.94-7.97 (dd, Ar-1H)

In the examples stated below describing composition comprising the novel salts of the present invention, the quantity stated for unit dosage form is the equivalent dose of the compound of Formula-II. The tablet/capsule compositions disclosed herein may optionally be coated by film forming polymer or enteric polymer known to the art.

Example-5: Tablet

S. No.	Ingredient	Quantity/tablet (mg)
1.	Compound of Formula-III	100.0
2.	Microcrystalline cellulose	310.0
3.	Lactose	100.0
4.	Croscarmellose sodium	20.0
5.	Isopropyl alcohol	Lost in processing
6.	Hydrogenated castor oil	7.5
7.	Purified talc	7.5
8.	Colloidal silicon dioxide	7.5

Procedure:

i) Compound of Formula-III, Lactose, Microcrystalline cellulose and Croscarmellose sodium were sifted through #40 sieve and were mixed together.

ii) The blend of step (i) was granulated by using Isopropyl alcohol.

iii) The wet mass of step (ii) was sifted through #24 sieve and granules obtained were dried.

iv) Hydrogenated castor oil, Purified talc and Colloidal silicon dioxide were sifted through #40 sieve and were mixed together.

v) Granules of step (iii) were mixed with the mixture of step (iv).

vi) The material of step (v) was compressed into tablets by using a tablet compression machine.

Example-6: Capsule

S. No.	Ingredient	Quantity/capsule (mg)
1.	Compound of Formula-IV	75.00
2.	Magnesium carbonate	150.00
3.	Dicalcium phosphate	131.25
4.	Crospovidone	30.00

5.	Magnesium stearate	10.00

Procedure:

i) Compound of Formula-IV, Magnesium carbonate, Dicalcium phosphate, Crospovidone, and Magnesium stearate were sifted through #40 sieve and were mixed together.

ii) The blend of step (i) was compacted and the compacts were passed through #30 sieve.

iii) The granules of step (ii) were lubricated with #60 sieve passed Magnesium stearate.

iv) The material of step (iii) was filled into hard gelatin capsule.

Example-7: Injection

S. No.	Ingredient	Quantity/ 100 ml
1.	Polyethylene glycol (PEG-400)	30.0
2.	Propylene glycol	20.0
3.	Glycine buffer pH 11.3	35.0
4.	Compound of Formula-V	2.5 g
5.	Sodium hydroxide (NaOH) solution 4.0% w/v	10.0

Procedure:

i) Specified quantity (30.0 ml) of PEG-400 was taken into a vessel.

ii) Propylene glycol (20.0 ml) was added to step (i) with continuous stirring using mechanical stirrer.

iii) About 30.0 ml of the Glycine buffer pH 11.3 was added to the step (ii) with continuous stirring to form a homogeneous mixture.

iv) Weighed amount of Compound of Formula-V (2.5 g) was passed through #60 sieve and was added to the step (iii) with continuous stirring.

v) Specified quantity (10.0 ml) of Sodium hydroxide (NaOH) 4.0% w/v solution was added to the step (iv) with continuous stirring to form a homogeneous solution.

vi) The solution of step (v) was mixed for about 30 minutes by continuous stirring.

vii) Remaining quantity of Glycine Buffer pH 11.3 was added to make up volume to 100 ml.

viii) The solution of step (vii) was mixed for about 10 minutes by continuous

stirring.

ix) Final pH was adjusted to 10.0 by adding Sodium hydroxide (NaOH) 4.0% w/v solution.

x) The solution of step (ix) was mixed for about 10 minutes by continuous stirring.

Example-8: Modified release Tablet

S. No.	Ingredient	Quantity/tablet (mg)
1.	Compound of Formula-VI	200.00
2.	Cetirizine	5.00
3.	Lactose	120.00
4.	Sodium starch glycollate	30.00
5.	Hydroxypropyl methylcellulose	67.00
6.	Isopropyl alcohol	Lost in processing
7.	Colloidal silicon dioxide	2.00
8.	Hydrogenated vegetable oil	2.00

Procedure:

i) Compound of Formula-VI, Cetirizine, Lactose and Sodium starch glycollate were sifted through #30 sieve and were mixed together.

ii) Hydroxypropyl methylcellulose was dissolved in Isopropyl alcohol to obtain a homogeneous dispersion.

iii) The blend of step (i) was granulated with the dispersion of step (ii).

iv) The granules of step (iii) were dried and were sifted through #24 sieve.

v) Colloidal silicon dioxide and Hydrogenated vegetable oil were sifted through #40 sieve.

vi) The material of step (v) was mixed with the material of step (iv) and compressed into tablets.

Example-9: Oral Liquid

S. No.	Ingredient	Quantity (mg/100 ml)
1.	Compound of Formula-VII	500.0
2.	Citric acid monohydrate	1.5
3.	Hydroxyethyl cellulose	20.0
4.	Sorbitol solution (70% w/v)	50.0

5.	Saccharin sodium	0.5
6.	Sodium benzoate	1.0
7.	Raspberry flavor	q.s.
8.	Purified water	q.s. to 100 ml

Procedure:

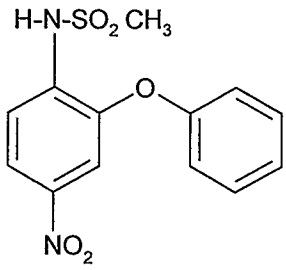
i) Compound of Formula-VII and Hydroxyethyl cellulose were sifted through #40 sieve and were blended together.

ii) Citric acid monohydrate, Saccharin sodium, Sodium benzoate, Raspberry flavor and Sorbitol solution were dispersed together in Purified water.

iii) The material of step (i) was added with continuous stirring to the material of step (ii) and a homogeneous suspension was obtained.

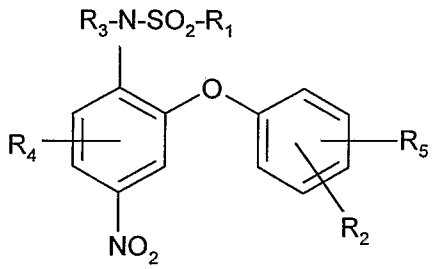
We claim:

1. Novel derivatives of N-(4-Nitro-2-phenoxy-phenyl)methane-sulfonamide having the following formula (Formula-1) and their pharmaceutically acceptable salts, esters, amides, polymorphs, solvates, hydrates, analogues, enantiomers, tautomeric forms or mixtures thereof:



Formula-I

2. The derivatives as claimed in claim 1, wherein the derivatives have the general formula (Formula-II):



Formula-II

Wherein:

R_1= an alkyl group 1-3 carbon atomic number, cycloalkyl group 3-6 atomic number, a phenyl group, or a substituted phenyl group, more particularly acetylaminophenyl group, or an aromatic heterocyclic group preferably having a 5-membered or 6-membered ring comprising a N and/or S and/or O,

R_2= a phenyl group, a halophenyl group, an amino group, a lower alkyl amino group, an allyl group, a vinyl group, an amino acid group, a lower N-substituted carboxy alkyl, or a lower N,N-disubstituted carboxy alkyl group, or an aromatic heterocyclic group preferably having a 5-membered or 6-membered ring comprising a N and/or S and/or O,

R_3 = -H,

$-CH_2COOH$ or its water soluble base addition salts,

$-CH_2-(CH_2)_n-COOH$, where n = 1-4 or their physiologically acceptable organic or inorganic base addition salts,

$-CO-CHX-NH_2$ (X is alkyl, a substituted alkyl, an aryl, a substituted aryl, a heterocyclic compound, or a physiologically acceptable organic or inorganic acid salt), or

- an aromatic heterocyclic group preferably having a 5-membered or 6-membered ring comprising a N and/or S and/or O, and

R_4= hydrogen, halogen, lower alkyl, an aryl or a substituted aryl, or a heterocyclic group.

R_5 = hydroxyl or an alkoxy group.

3. A process for the preparation of novel derivatives according to claim 1, wherein the said process comprises treating N-(4-Nitro-2-phenoxy-phenyl)methane-sulfonamide with suitable solvents and base to produce the derivatives.

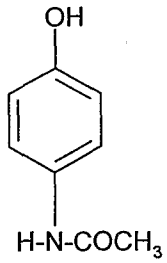
4. A process for the preparation of novel derivatives according to claim 3, wherein the solvent is selected from a group comprising dipolar aprotic solvents, aliphatic cyclic ethereal solvents or non polar water immiscible solvents mixtures thereof.

5. A process for the preparation of novel derivatives according to claim 3, wherein the base is selected from a group comprising organic aminic base, alkali metal hydroxides and/or mild bases or mixtures thereof.

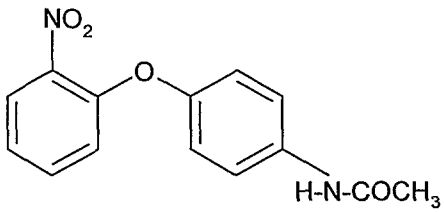
6. A process for the preparation of novel derivatives according to claim 5, wherein the mild base is selected from a group comprising alkali metal carbonates and/or sodium and/or potassium methoxide, sodium and/or potassium ethoxide, sodium and/or potassium hydride, sodium and/or potassium t-butoxide or mixtures thereof.

7. A process for the preparation of novel derivative herein referred to as compound of Formula III according to claim 3, wherein the process comprises of the following steps:

i) reacting a compound of the Formula-VIII, namely 4-hydroxyacetanilide, with 2-halonitrobenzene, in the presence of a base and in the absence or presence of the solvent to yield a compound represented by Formula-IX,



Formula-VIII



Formula-IX

ii) reducing the – NO_2 (nitro) group of compound of Formula-IX, to – NH_2 (amino) group by using conventional reducing agents in a suitable alcoholic solvent at a temperature ranging between 0°C to reflux temperature of the solvent used so as to yield required amino derivative in a suitable physiologically acceptable organic solvent,

iii) sulphonating the compound of step (ii) with a suitable sulphonating agent selected from a group comprising CH_3SO_2Z and/or $(CH_3SO_2)_2O$, wherein Z is selected from the group comprising of halogen atom in the presence of a pharmaceutically acceptable organic solvent, and in the presence or absence of pharmaceutically acceptable organic or inorganic base or by means of a suitable acid acceptor, and

iv) subjecting the intermediate so obtained as per the method of step (iii) to a nitrating mixture selected from the group comprising chloroform/nitric acid, or acetic acid/nitric acid or sulphuric acid/nitric acid for the introduction of nitro group at the required position by means of nitration so as to get the compound represented by Formula-III.

8. A process for the preparation of novel derivative herein referred to as compound

of Formula IV according to claim 3, wherein the process comprises reacting N-(4-Nitro-2-phenoxy phenyl) methane sulfonamide, i.e. nimesulide, of Formula-I as herein described as starting material with Q-alkyl-COOR5, wherein Q belongs to the class of halo atoms, and alkyl refers to lower alkyl, and R5 is H and/or lower alkyl selected from a group comprising methyl, ethyl, propyl, t-butyl, lower aromatic, in the presence or absence of a suitable physiologically acceptable organic base and in a suitable organic solvent.

9. A process for the preparation of novel derivative herein referred to as compound of Formula V according to claim 3, wherein the process comprises reacting N-(4-Nitro-2-phenoxy phenyl) methane sulfonamide of Formula-I or its alkali metal salt, as starting material with Z-OC-CHX-NH2 (with protected NH2 group), wherein X is defined herein and Z belongs to the class of halo atoms, in the absence or presence of an organic aminic base in a suitable organic solvent.

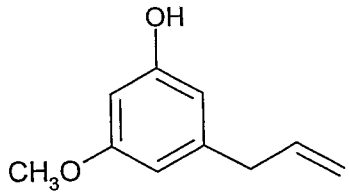
10. A process for the preparation of novel derivative herein referred to as compound of Formula VI according to claim 3, wherein the process comprises of the following steps:

i) reacting 2-phenoxy aniline, with sulphonating agent $ArSO_2Z$, wherein Ar is selected from the group comprising aryl or substituted aryl and Z belongs to the class of halogen atoms in the presence of an organic aminic base in a suitable organic solvent to give sulfonanilide, and

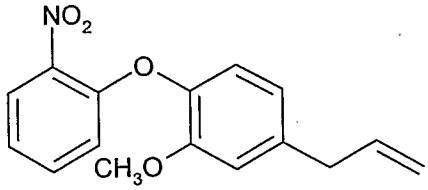
ii) subjecting the said sulfonanilide to nitrating mixture for the introduction of nitrate group at the desired position by means of nitration methods selected from a group comprising chloroform/nitric acid or in acetic acid/nitric acid or sulphuric acid/nitric acid so as to get the compound represented by Formula-VI.

11. A process for the preparation of novel derivative herein referred to as compound of Formula VII according to claim 3, wherein the process comprises of the following steps:

i) reacting a compound of the Formula-X, namely 4-allyl-2-methoxyphenol, with 2-halonitrobenzene in the presence of a base and in the absence or presence of the solvent to yield a compound represented by Formula-XI,



Formula-X



Formula-XI

ii) reducing the – NO_2 (nitro) group of the compound of formula-XI to – NH_2 (amino) group by using conventional reducing agents at a temperature ranging between 0°C to reflux temperature of the solvent used so as to yield required amino derivative in a suitable physiologically acceptable organic solvent,

iii) sulphonating the compound obtained in amino form in step (ii) with a suitable sulphonating agent selected from a group comprising CH_3SO_2Z and/or $(CH_3SO_2)_2O$, wherein Z is selected from the group comprising of halogen atom, in the presence of a pharmaceutically acceptable organic solvent and in the presence or absence of pharmaceutically acceptable organic or inorganic base or by means of a suitable acid acceptor, and

iv) subjecting the intermediate obtained as per the method of step (iii) to nitrating mixture selected from the group comprising chloroform/nitric acid, or acetic acid/nitric acid or sulphuric acid/nitric acid for the introduction of nitro group at the required position by means of nitration so as to get the compound represented by Formula-VII.

12. A method of using the novel derivatives according to claim 1, which comprises administering to a subject in need thereof an effective amount of such novel derivatives.

13. Use of novel derivatives according to claim 1 in the management of inflammation and/or pain associated with osteoarthritis, respiratory tract

inflammation, postoperative pain, inflammation of the ear, nose and throat, headache, toothache, post-traumatic pain, fever, or other associated disorders.

14. A pharmaceutical composition comprising the derivatives according to claim 1, alongwith pharmaceutically acceptable excipient(s).

15. A pharmaceutical composition comprising the derivatives according to claim 1, which additionally comprises other pharmacologically active ingredient.

16. The derivatives according to claim 1, which can be in the form of an associate or a complex or inclusion compounds optionally with pharmaceutically acceptable excipient(s).

17. A pharmaceutical composition as claimed in claim 14, wherein the pharmaceutically acceptable excipients are selected from a group comprising diluents, disintegrants, binders, fillers, bulking agents, anti-adherents, anti-oxidants, buffering agents, colorants, flavoring agents, coating agents, plasticizers, organic solvents, stabilizers, preservatives, lubricants, glidants, chelating agents, either alone or in combination thereof.

18. A composition according to claim 14, wherein the composition may be administered orally, parenterally or topically, in the form of tablet, capsule, drops, injection, suppository, patch, ointment and the other formulations suitable for oral administration, injection or topical application.

19. A process for the preparation of pharmaceutical composition according to claim 14, comprising the novel derivatives with one or more pharmaceutically acceptable excipient(s), optionally with other active ingredients which comprises treating the derivatives with one or more other pharmaceutically acceptable excipient(s), optionally with other active ingredient and formulating into a suitable dosage form.

20. A method of using the pharmaceutical composition according to claim 14 for the prophylaxis, amelioration and/or treatment of inflammation and/or pain and other associated disorders which comprises administering to a subject in need

thereof an effective amount of such composition.

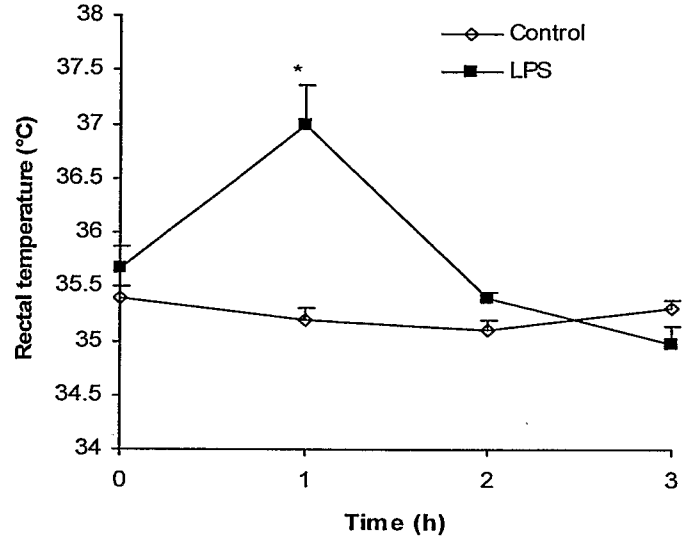
21. A method according to claim 20, wherein the inflammation and/or pain and other associated disorders is selected from a group comprising osteoarthritis, respiratory tract inflammation, postoperative pain, inflammation of the ear, nose and throat, headache, toothache, post-traumatic pain, fever.

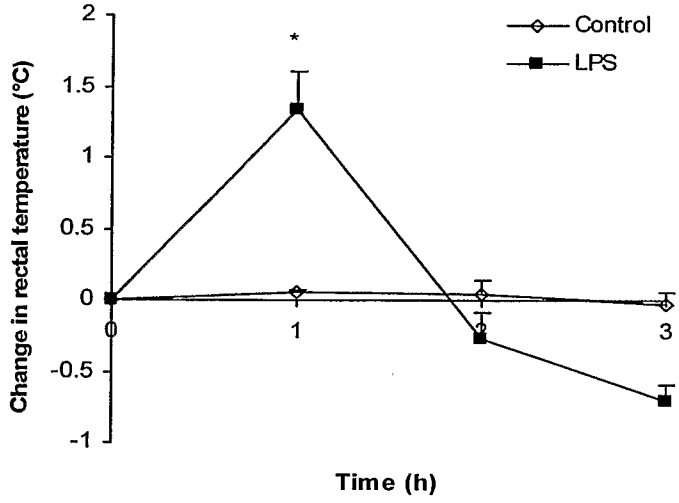
22. Use of the pharmaceutical composition according to claim 1 for the manufacture of a medicament for the prevention treatment and/or amelioration of inflammation and/or pain and other associated disorders.

23. The novel derivatives and process for the preparation of novel derivatives substantially as herein described and illustrated by the examples.

24. The pharmaceutical composition and process for the preparation of a pharmaceutical composition comprising the novel derivatives substantially as herein described and illustrated by the examples.

Figure-1:

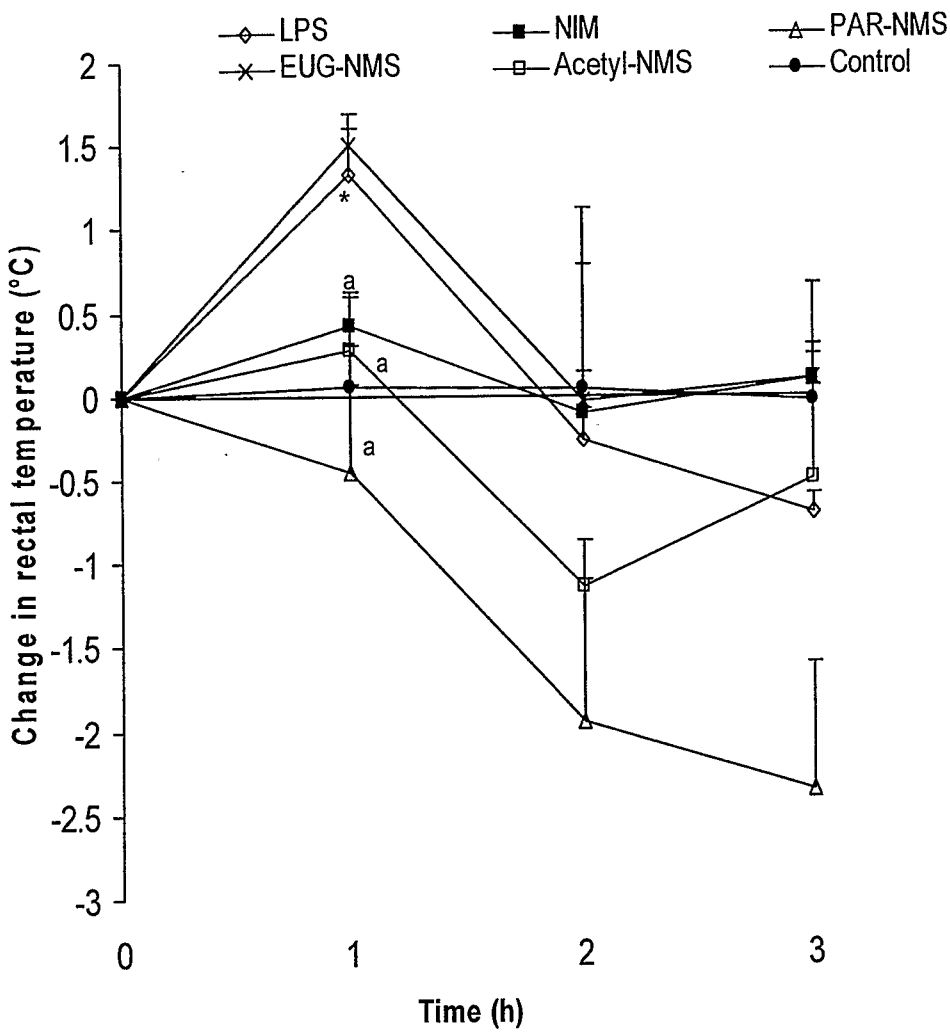




Each point represents the mean ± S.E.M. (n=3-6).

*P < 0.05 as compared to control group.

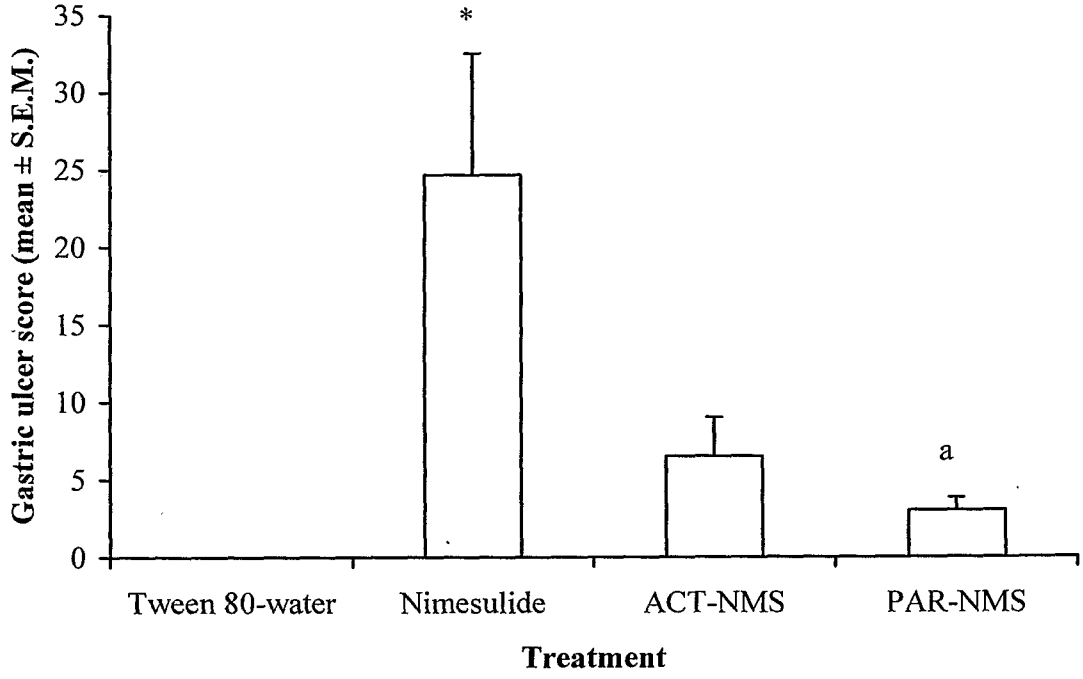
Figure-2:



Each point represents absolute rectal temperature as mean ± S.E.M. (n=3-6).

*P < 0.05 as compared to control group; aP < 0.05 as compared to LPS-treated group.

Figure-3:



*P<0.05 as compared to Tween 80-water treated rats; aP<0.05 as compared to Nimesulide group.