

Study of Anthranilic Acid Derivatives: Mefenamic Acid and Its Various Analogues

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Abstract Anthranilic acid derivatives are direct structural analogs of salicylic acid derivatives. They possess analgesic, anti-inflammatory, and antipyretic activity. They are similar to pyrazolones in terms of analgesic and antipyretic activity, yet they exceed the anti-inflammatory activity of salicylates. The mechanism of action of this series of nonsteroid, anti-inflammatory analgesics is not conclusively known. One of the early advances in the search for nonnarcotic analgesics was centered in the N-arylanthranilic acids. The outstanding characteristic of mefenamic acid is primarily anti-inflammatory, and secondarily, some possess analgesic properties.

Keywords: anthranilic acid derivatives, analgesic, anti-inflammatory, antipyretic nonsteroid

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1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of pain and inflammation. Mostly NSAIDs are non selectively inhibit the two isoforms of the cyclooxygenase (COX-1 and COX-2) even celecoxib and derivatives are found as selective to directly target COX-2 and thus prevent the metabolism of cellular arachidonic acid (AA) and the upregulation of prostaglandin formation, which otherwise lead to an increase of vascular permeability, edema, hyperalgesia, pyrexia and inflammation [1]. In addition to COX, the 5-lipoxygenase (5-LO) enzyme is another key enzyme which is involved in the AA cascade. Inflammatory mediators leukotrienes, produced through the 5-LO enzyme pathway, may also contribute to both inflammation and NSAIDs induced side effects. For these reasons, compounds that are dual inhibitors of both COX and 5-LO are being studied as potential analgesic and anti-inflammatory agents with an improved safety profile in comparison to NSAIDs [2]. Currently, various chemical families of dual COX/5-LO inhibitors can be found in the scientific literatures [3]. In the 1980's, hydrazone-type containing compounds such as BW 755c (1) and CBS 1108 (2) (Fig 1) were described as dual COX/5-LO inhibitors which present analgesic and anti-inflammatory activities. In fact, some evidences suggest that the hydrazone moiety present in derivative 3 (Figure 1) possess the inhibition of COX. According to these results, analgesic profile of new series of heterocyclic N-acylarylhydrazones 4-6 (Figure 2) has been previously described [4,5]. In addition to these compounds, there are some reports about importance of fenamate structures in dual inhibition of COX/5-LO by substitution of their

carboxylic acid moiety with some acidic heterocycles, namely 1,3,4-oxadiazole-2-thione (7) and 1,3,4-thiadiazole-2-thione (8) (Figure 3) eg in mefenamic acid [1,6]. Thus, the carboxylic acid moiety of mefenamic acid, a known NSAID drug, with an N-arylhydrazone group in the hope of obtaining additional inhibitors of cellular AA metabolism.

2. Mefenamic Acid

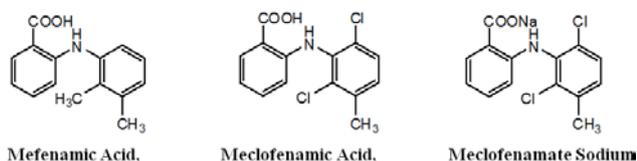
N-(2,3-Xylyl) anthranilic acid; 2-[(2, 3-dimethylphenyl) amino]- Benzoic acid. It is synthesized by the reaction of the potassium salt of 2-bromobenzoic acid with 2,3-dimethylaniline in the presence of copper (II) acetate. It is used for the same indications as flufenamic acid. Synonyms for this drug are parkemed, ponstan, ponstel, and others. It might be prepared by the condensation of o-chlorobenzoic acid with 2, 3-xylidine in the presence of potassium carbonate to give the potassium salt of mefenamic acid, which on treatment with hydrochloric acid yields the official compound. It is an analgesic drug usually indicated for the treatment of primary dysmenorrhea, mild pain and for pain due to dental extractions. Dose: Usual, adults, children over 14 years of age, oral, 500 mg, followed by 250 mg 4 times daily. (Caution : Must not be used for more than 7 days). The precise mechanism of action is assumed to be related to its ability to block prostaglandin (PG) synthetase almost completely. Besides, there are several evidences in literature(s) with regard to its anti-UV erythema activities. It definitely shows much decreased incidence of gastrointestinal bleeding, a prominent drawback of such drugs, when compared to 'aspirin'. Besides, it has been duly approved for the control and management of primary dysmenorrhea, that is believed to be caused by

overwhelming concentrations of endoperoxides as well as prostaglandins (PG) (AHFS drug information 2007).

It occurs as an off-white crystalline powder that is insoluble in water and slightly soluble in alcohol. It appears to be the first genuine antiphlogistic analgesic discovered since aminopyrine. Because it is believed that aspirin and aminopyrine owe their general purpose analgesic efficacy to a combination of peripheral and central effects. Wide variety of arylanthranilic acids were screened for analgesic activity if they showed significant anti-inflammatory action. The combination of both effects is a rarity among these compounds. The mechanism of analgesic action is believed to be related to the ability to block prostaglandin synthetase. No relationship to lipid. plasma distribution, partition coefficient, or pK, has been noted [2,7].

3. Meclofenamate Sodium or Meclofenamic Acid

Monosodium N-(2, 6-dichloro-*m*-tolyl) anthranilate monohydrate; Benzoic acid, 2-[2, 6-(dichloro-3-methylphenyl) amino]-, monosodium salt. It may be prepared by the Ulman Condensation of *o*-iodobenzoic acid with 2, 6-dichloro-*m*-toluidine in the presence of copper-bronze resulting into the formation of meclofenamic acid which on neutralization with equimolar proportion of sodium hydroxide yields meclofenamate sodium. It possesses analgesic, anti-inflammatory, and antipyretic properties [8]. It is used for the treatment of acute and chronic rheumatoid arthritis and osteoarthritis. Dose: Usual, oral, 200 to 400 mg daily in 3 or 4 equal doses. Meclofenamic acid, N-(2,6-dichloro-*m*-tolyl)anthranilic acid, is synthesized analogous to flufenamic acid, by the reaction of potassium salt of 2-bromobenzoic acid with 2,6-dichloro-3-methylaniline in the presence of copper (II) bromide in a mixture of *N*-ethylmorpholine and diglyme. It is used for the same conditions as flufenamic acid. A synonym for this drug is movens. The 2,6-dichloro derivative of mefenamic acid, as its sodium salt; and exerts its most predominant side effects, such as: diarrhea, and gastro intestinal disorders [8].

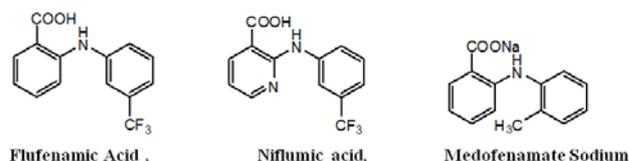


4. Flufenamic Acid

N-(α,α,α -Trifluoro-*m*-tolyl)-anthranilic acid; 2-[[3-(trifluoro-methyl) phenyl] amino]-Benzoic acid. It has analgesic, anti-inflammatory and antipyretic actions. It is employed in the treatment of rheumatic disorders and dysmenorrhoea. Dose: 400 to 600 mg per day in divided doses. It is synthesized by the reaction of 2-chlorobenzoic acid with 3-trifluoromethylaniline in the presence of potassium carbonate and copper filings. Flufenamic acid is used for moderate pain and dysmenorrhoea, but it should not be used for more than 1 week due to the possibility of

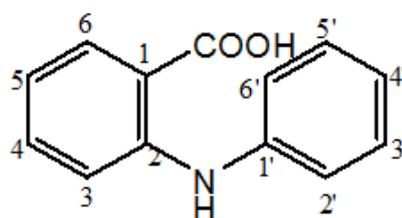
nephrotoxicity, gastrointestinal toxicity, and anemia. It is frequently used in combination with the anticoagulant warfarin, the effect of which is strengthened when combined with flufenamic acid. Synonyms for this drug are arlef, flexocutan, romazal, and others. It is a trifluoromethyl analogue of anthranilic acid, that exerts its three-in-one pharmacological actions *viz.*, antipyretic, analgesic, and anti-inflammatory. It finds its abundant usage in dysmenorrhoea and various types of rheumatic disorders. However, the exact and precise mechanism of antipyretic action of the N-aryl anthranilic acid structural variants has not yet been established. There exists no relationship to lipid plasma distribution, partition coefficient or pKa values of these types of drugs *vis-a-vis* their antipyretic activity.

Niflumic acid: Niflumic acid, 2-3-(trifluoromethyl) anilino nicotinic acid, is synthesized either by the reaction of 2-chloronicotinic acid with 3-trifluoromethylaniline, or 2-aminonicotinic acid with 1-bromo-3-trifluoromethylbenzene. It is used same as mefenamic acid. Synonyms for this drug are actol, flunir, nifluril, and others [9,10].



For nonsteroidal anti-inflammatory carboxylic acids such as mefenamic acid or N-(7-chloro-4-quinolyl)anthranilic acid [11], glyceryl esters are claimed to be less irritating. Alternatively, the ulcerogenicity of indomethacin derivatives was reduced by formation of the ester with glycolic acid [12] or the peptide with serine [13]. Another indomethacin-related anti-inflammatory drug, sulindac, is an inactive sulfoxide and becomes only activated after absorption and reduction into the corresponding sulfide. Thus the initial exposure of gastric and intestinal mucosa to the active drug is circumvented. Mefenamic acid in a dose of 250 mg is superior to 600 mg of aspirin as an analgesic and doubling the dose sharply increases its efficacy. A study examining this drug relative to gastrointestinal bleeding indicated a lower incidence of this side effect than by aspirin. 34 Diarrhea, drowsiness, and headache have accompanied its use. The possibility of blood disorders has prompted limitation of its administration to 7 days. It is not recommended (children or during pregnancy). It has been approved for use in the management of primary dysmenorrhoea (PD) which is thought to be caused by excessive concentrations of prostaglandins and endoperoxides.

Meclofenamate Sodium: Sodium N-(2,6-dichloro-*m*-tolyl)anthranilate in 50 and 100 mg capsules for use in the treatment of acute and chronic RA. The most significant side effects are gastrointestinal, including diarrhea



5. Structure Activity Relationship

Substitution on the anthranilic acid ring generally reduced the activity.

Substitution on the N-aryl ring can lead to conflicting results.

In the UV erythema assay for the anti-inflammatory activity the order of activity was generally 3'>2'>4' for mono substitution with CF₃ group (flufenamic acid) being particular patent. The opposite order of activity was observed in the rat paw oedema assay, the 2'Cl derivative being more potent than 3'Cl analogue.

In di-substituted derivatives, where the nature of two substituent is the same, 2',3' di-substitution appear to be the most effective (mefenamic acid).

The NH moiety of anthranilic acid appears to be essential for activity since replacement of NH functional group with O, CH₂, S, SO₂, NH₃ or NCOCH₃ functionalities significantly reduce the activity.

The position of acidic function is critical for activity, anthranilic acid derivatives are active where as meta and para benzoic acid analogues are not. Replacement of carboxylic acid functions with the isosteric tetrazole has little effect on the activity.

Mefenamic Acid Warning (s): Cardiovascular Risk; Possible increased risk of serious (sometimes fatal) cardiovascular thrombotic events (e.g., MI, stroke). Risk may increase with duration of use. Individuals with cardiovascular disease or risk factors for cardiovascular disease may be at increased risk. Contraindicated for the treatment of pain in the setting of CABG surgery. GI Risk and Increased risk of serious (sometimes fatal) GI events (e.g., bleeding, ulceration, perforation of the stomach or intestine). Serious GI events can occur at any time and may not be preceded by warning signs and symptoms [7,14,15]. Geriatric individuals are at greater risk for serious GI events [9,16-23].

Uses for Mefenamic Acid: Consider potential benefits and risks of mefenamic acid therapy as well as alternative therapies before initiating therapy with the drug. Use lowest possible effective dosage and shortest duration of therapy consistent with patient's treatment goals [15,24-39].

Pain: Relief of mild to moderate pain in patients ≥14 years of age when the duration of therapy ≤1 week. **Dysmenorrhea:** Treatment of primary dysmenorrhea. **Fever:** Has been used for reduction of fever associated with infection in children; routine use as an antipyretic not recommended because of potential adverse effects.

Mefenamic Acid Dosage and Administration: Consider potential benefits and risks of mefenamic acid therapy as well as alternative therapies before initiating therapy with the drug. **Oral Administration:** Administer orally; May be administered in divided doses up to 4 times daily. **Dosage:** To minimize the potential risk of adverse cardiovascular and/or GI events, use lowest effective dosage and shortest duration of therapy consistent with the patient's treatment goals. Adjust dosage based on individual requirements and response; attempt to titrate to the lowest effective dosage. **Pediatric Patients: Pain (Oral)** Adolescents ≥14 years of age should receive dosage recommended for adults. **Adults: (Pain) Oral** For mild to moderate pain in adults, 500 mg initially followed by 250 mg every 6 hours as necessary. **Dysmenorrhea: Oral** For

relief of primary dysmenorrhea in adults, 500 mg initially followed by 250 mg every 6 hours as necessary. Initiate at onset of bleeding and associated symptoms; treatment should not be necessary for >2-3 days.

6. Prescribing Limits

Pediatric Patients Pain (Oral) Duration of therapy usually should not exceed 1 week.

Adults Pain (Oral) Duration of therapy usually should not exceed 1 week.

Dysmenorrhea: Oral Therapy should not be necessary for more than 2-3 days.

Special Populations

Hepatic Impairment: Dosage reduction may be required.

Renal Impairment: Dosage reduction may be required if used in patients with renal impairment. Use not recommended in patients with preexisting renal disease or substantial renal impairment.

Geriatric Patients: Select dosage carefully since may be more likely to have decreased renal function.

Cautions for Mefenamic Acid

Contraindications: Known hypersensitivity to mefenamic acid or any ingredient in the formulation. History of asthma, urticaria, or other sensitivity reaction precipitated by aspirin or other NSAIDs. Treatment of perioperative pain in the setting of CABG surgery. Active ulceration or chronic inflammation of upper or lower GI tract. Preexisting renal disease.

7. Warnings/Precautions

Cardiovascular Effects: Selective COX-2 inhibitors have been associated with increased risk of cardiovascular events (e.g., MI, stroke) in certain situations [40,41]. Several prototypical NSAIDs also have been associated with increased risk of cardiovascular events [42-44]. Information not available on risk associated with mefenamic acid at this time [43-45]. Use NSAIDs with caution and careful monitoring (e.g., monitor for development of cardiovascular events) and at the lowest effective dosage for the shortest duration necessary. Short-term use to relieve acute pain, especially at low dosages, does not appear to be associated with increased risk of serious cardiovascular events (except immediately following CABG surgery). No consistent evidence that concomitant use of low-dose aspirin mitigates the increased risk of serious adverse cardiovascular events associated with NSAIDs. Hypertension and worsening of preexisting hypertension reported; either event may contribute to the increased incidence of cardiovascular events. Use with caution in patients with hypertension; monitor BP. Impaired response to certain diuretics may occur. Fluid retention and edema reported. Caution in patients with fluid retention or heart failure.

GI Effects: Serious GI toxicity (e.g., bleeding, ulceration, perforation) can occur with or without warning symptoms; increased risk in those with a history of GI bleeding or ulceration, geriatric patients, smokers, those with alcohol dependence, and those in poor general health. For patients at high risk for complications from NSAID-

induced GI ulceration (e.g., bleeding, perforation), consider concomitant use of misoprostol [46-49]; alternatively, consider concomitant use of a proton-pump inhibitor (e.g., omeprazole) [38,46] or use of an NSAIA that is a selective inhibitor of COX-2 (e.g., celecoxib).

Renal Effects: Direct renal injury, including renal papillary necrosis, reported in patients receiving long-term NSAID therapy. Potential for overt renal decompensation. Increased risk of renal toxicity in patients with renal or hepatic impairment or heart failure, in geriatric patients, in patients with volume depletion, and in those receiving a diuretic, ACE inhibitor, or angiotensin II receptor antagonist [47].

8. Sensitivity Reactions

Hypersensitivity Reactions: Anaphylactoid reactions reported. Immediate medical intervention and discontinuance for anaphylaxis. Avoid in patients with aspirin triad (aspirin sensitivity, asthma, nasal polyps); caution in patients with asthma.

Dermatologic Reactions: Serious skin reactions (e.g., exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis) reported; can occur without warning. Discontinue at first appearance of rash or any other signs of hypersensitivity (e.g., blisters, fever, pruritus).

General Precautions

Hepatic Effects: Severe reactions including jaundice, fatal fulminant hepatitis, liver necrosis, and hepatic failure (sometimes fatal) reported rarely with NSAIA. Elevations of serum ALT or AST reported. Monitor for symptoms and/or signs suggesting liver dysfunction; monitor abnormal liver function test results. Discontinue if signs or symptoms of liver disease or systemic manifestations (e.g., eosinophilia, rash) occur.

Hematologic Effects: Anemia reported rarely. Determine hemoglobin concentration or hematocrit in patients receiving long-term therapy if signs or symptoms of anemia occur. May inhibit platelet aggregation and prolong bleeding time.

Ocular Effects: Visual disturbances reported; ophthalmic evaluation recommended if visual changes occur [47].

Other Precautions: Not a substitute for corticosteroid therapy; not effective in the management of adrenal insufficiency. May mask certain signs of infection. Obtain CBC and chemistry profile periodically during long-term use [9,16-23].

Specific Populations

Pregnancy: Category C. Avoid use in third trimester because of possible premature closure of the ductus arteriosus.

Lactation: Distributed into milk. Discontinue nursing or the drug (AHFS drug information 2007; US Food and Drug Administration. 2005; Buchanan et al. 1968).

Pediatric Use: Safety and efficacy not established in children <14 years of age.

Geriatric Use: Use with caution in patients ≥ 65 years of age. Geriatric adults appear to tolerate therapy less well (e.g., possible higher incidence of adverse GI effects, greater risk of developing renal decompensation) than younger individuals. Fatal adverse GI effects reported more frequently in geriatric patients than younger adults. Substantially eliminated by kidneys; periodic monitoring of renal function may be useful since geriatric patients are more likely to have decreased renal function (Geriatric Patients under Dosage and Administration and Renal Impairment under Cautions). Renal Impairment: Use not recommended in patients with preexisting renal disease or substantial renal impairment. Common Adverse Effects: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal), vomiting, abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, tinnitus [47].

Interactions for Mefenamic Acid

Protein-bound Drugs: Possible pharmacokinetic interaction; potential for mefenamic acid to be displaced from binding sites by, or to displace from binding sites, other protein-bound drugs (e.g., oral anticoagulants, hydantoins, salicylates, sulfonamides, and sulfonylureas) (9,20). Observe for adverse effects if used with other protein-bound drugs.

Drugs Affecting Hepatic Microsomal Enzymes: Inhibitors of CYP2C9: possible altered safety and efficacy of mefenamic acid (First Horizon Pharmaceutical Corporation. 2006).

Specific Drugs

Drug	Interaction	Comments
ACE inhibitors	Reduced BP response to ACE inhibitor possible Possible deterioration of renal function in individuals with renal impairment	Monitor BP
Angiotensin II receptor antagonists	Reduced BP response to angiotensin II receptor antagonist possible Possible deterioration of renal function in individuals with renal impairment	Monitor BP
Antacids (magnesium-containing)	Increased peak plasma concentrations and AUC of mefenamic acid	
Anticoagulants (e.g., warfarin)	Possible bleeding complications	Use with caution; frequent monitoring of PT advised
Aspirin	Increased risk of GI ulceration or other complications No consistent evidence that low-dose aspirin mitigates the increased risk of serious cardiovascular events associated with NSAIA	Concomitant use generally not recommended
Diuretics (furosemide, thiazides)	Reduced natriuretic effects possible	Monitor for diuretic efficacy and renal failure
Lithium	Increased plasma lithium concentrations (Nonsteroidal anti-inflammatory drug interactions)	Monitor for lithium toxicity (Nonsteroidal anti-inflammatory drug interactions).
Methotrexate	Possible toxicity associated with increased plasma methotrexate concentrations during concomitant NSAIA use.	Caution advised

9. Mefenamic Acid Pharmacokinetics

Absorption and Bioavailability: Rapidly absorbed following oral administration. Peak plasma concentrations usually attained within 2–4 hours [47]. Effect of food on rate and extent of absorption not known. Appears to cross the placenta. Distributed into milk in small amounts.

Plasma Protein Binding: >90%.

Elimination and Metabolism: Metabolized by CYP2C9 to 3'-hydroxymethyl mefenamic acid; further oxidation to 3'-carboxymefenamic acid may occur. Mefenamic acid and its metabolites also are glucuronidated [47].

Elimination Route: Excreted in urine (52%) primarily as glucuronic acid conjugates of the drug and its metabolites and in feces (<20%) [47].

Half-life: Mefenamic acid: approximately 2 hours. Half-lives of 3'-hydroxymethyl mefenamic acid and 3'-carboxymefenamic acid may be longer than parent compound [47].

Special Populations: Half-life 5 times longer in preterm infants compared with adults. In patients with renal or hepatic impairment, clearance of metabolites may be decreased. Not substantially removed by hemodialysis [47].

Stability and storage: Oral Capsules 20–25°C (may be exposed to 15–30°C) [47].

Actions: Inhibits cyclooxygenase-1 (COX-1) and COX-2 [33-37,39]. Pharmacologic actions similar to those of other prototypical NSAIDs; exhibits anti-inflammatory, analgesic, and antipyretic activity [47].

Advice to Patients: Importance of reading the medication guide for NSAIDs that is provided to the patient each time the drug is dispensed. Risk of serious cardiovascular events with long-term use [9,16,42,43,44,45]. Importance of notifying clinician if signs and symptoms of a cardiovascular event (chest pain, dyspnea, weakness, slurred speech) occur. Risk of GI bleeding and ulceration (Soll et al. 1991). Importance of notifying a clinician if signs and symptoms of serious adverse GI effects occur. Importance of discontinuing mefenamic acid and contacting clinician if rash or other signs of hypersensitivity (blisters, fever, pruritus) develop. Importance of seeking immediate medical attention if an anaphylactic reaction occurs. Risk of hepatotoxicity. Importance of discontinuing therapy and contacting a clinician immediately if signs and symptoms of hepatotoxicity (nausea, fatigue, lethargy, pruritus, jaundice, upper right quadrant tenderness, flu-like symptoms) occur. Importance of notifying clinician if signs and symptoms of unexplained weight gain or edema develop. Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed. Importance of avoiding mefenamic acid in late pregnancy (third trimester). Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs. Importance of informing patients of other important precautionary information.

N-Arylhydrazone derivatives of mefenamic acid: A series of N-Arylhydrazone derivatives of mefenamic acid (known NSAIDs) were studied as potential analgesic and anti-inflammatory agents. Most of the compounds induced significant reduction in the writhing response. Among

them, compounds **11**, **12**, **15**, **16**, **19**, **20**, and **21** were significantly more potent than mefenamic acid in the writhing test. The compounds **11**, **12**, **16**, **19** and **20** showed significant anti-inflammatory activity but their effect was weaker than mefenamic acid. The analgesic relative activity of some of these synthesized compounds is greater than mefenamic acid but they are not potent anti-inflammatory agents [50].

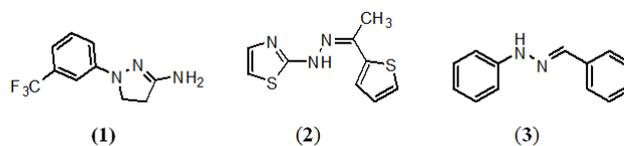


Figure 1. Structures of Compounds 1-3

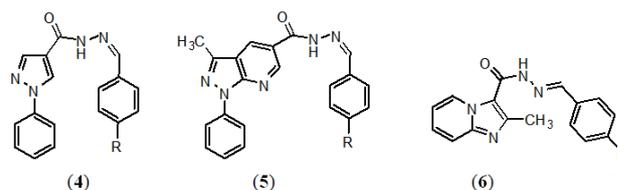


Figure 2. Structures of compounds 4-6

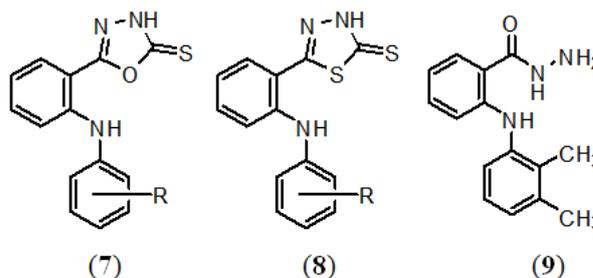
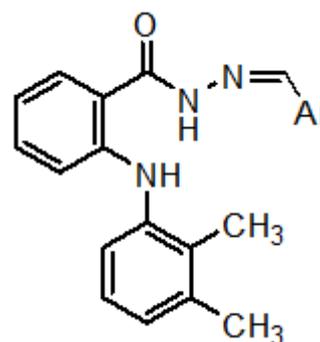


Figure 3. Structures of compounds 7, 8 and 9.

R = 2,6-di-Cl,3-Me or 3- or 2,3-diMe



Ar = 4-substituted phenyl, 2-Pyridyl, 3-pyridyl or 4-pyridyl

Figure 4. Structures of compounds 10-21

Compound	Ar	Compound	Ar
10	4-tolyl	16	4-chlorophenyl
11	4-fluorophenyl	17	4-N,N-dimethylaminophenyl
12	4-methoxyphenyl	18	4-pyridyl
13	Phenyl	19	3-pyridyl
14	4-hydroxyphenyl	20	2-pyridyl
15	4-nitrophenyl	21	4-bromophenyl

The compounds were administered intraperitoneally (i.p) (31 μmol/kg; 0.2 ml/20g). Mefenamic acid (31 μmol/kg, IP) (9) was used as standard drug under the same conditions.

10. Results

N-arylhydrazone derivatives of mefenamic acid (**10-21**) were evaluated for analgesic activity (fig 4). Except compounds **13**, **16**, **17** and **21**, all of them induced significant analgesic activity and among them 7 compounds significantly showed higher inhibitory effect on the writhing response in comparison to mefenamic acid as follow: (**10**, 71.1%), (**11**, 58.5%), (**14**, 46.7%), (**15**, 42.4%), (**18**, 67.9%), (**19**, 93.7%), (**20**, 50.9%), mefenamic acid (25.6%). These 7 compounds showed more analgesic activity in comparison to mefenamic acid. Compounds **10**, **11**, **15** and **18** as well as mefenamic acid induced significant anti-inflammatory activity after 3 and 4 h but none of the tested compounds was more active than mefenamic acid. Compound **19** showed significant anti-inflammatory activity after 1, 2 and 3h and after 1 h in comparison to mefenamic acid [50].

11. Discussion

The pharmacological results show a good analgesic profile in comparison to control and mefenamic acid. The most active derivatives **18**, **19** and **20** possess the pyridine ring at the aryl moiety of the arylhydrazone frame work [4]. The compounds possessing the 4-tolyl or 4-fluorophenyl moiety **10**, **11** respectively are among the most active compounds. But in other study 4-Bromophenyl and 4-N, N-dimethylaminophenyl have a major contribution to the analgesic activity [4,5, 51,52]. Compounds **19**, **21** are among the weakest structures. Some Narylhydrazone derivatives **4-6** have presented an important analgesic profile which found to be more influenced by the nature of phenyl ring substituent of the hydrazone sub-unit than the pattern of the heterocyclic ring of the N-acyl moiety [4]. Therefore, it is possible that replacement of these kinds of acyl groups with a fenamate structure has changed the mechanism of enzyme-receptor interaction and the importance of 4-substituents of phenyl rings at the aryl moiety of the aryl hydrazone frame work. Since in vivo activity depends on highly complex physiological interactions, therefore at this moment we are unable to rationalize all of pharmacological results. The anti-inflammatory evaluation of 7 most potent compounds showed that replacement of carboxylic acid group of mefenamic acid with Narylhydrazone moiety cannot produce any advantage in the anti-inflammatory properties of this drug. Most of the compounds had a similar bioavailability profile to mefenamic acid and compounds **10**, **11**, **15** and **18** were active after 3 and 4 h. Compound **19** showed significant anti-inflammatory effect. Therefore in spite of a relative high potency after 1h it does not have a good kinetic profile. The replacement of the acidic moiety of mefenamic acid with N-arylhydrazone moiety can create potent analgesic compounds [53,54]. Further studies are needed to explore the differences in the efficacy and safety of synthesized compounds.

Acknowledgement

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