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Synthesis of Few Xanthenedione Derivatives by Green Chemistry Method and Evaluation of Analgesic Activity of the Same

Manasi M. Kanhe
Lecturer, M. P. Deo Dharampeth Science College, Academic Institute, Nagpur, India

***Abstract*: Synthesis of few xanthenedione derivatives by green chemistry method is a unique concept in terms of preservation of nature from pollution, and synthesize the same analogues by new method over traditional method of synthesis of chemical compounds. The synthesized xanthenedione derivatives were then evaluated for their analgesic activity as an additional part of research work.**

***Introduction:* Synthesis of various derivatives by green chemistry synthesis method shows advantages of microwave method over the traditional conventional method and also microwave method requires less time for synthesis but synthesize equal quantity of compounds like traditional method.**

***Method:* Conventional method of synthesis of compound the reaction mixture is heated and this heating proceeds a surface usually inside surface of reaction vessels. The vessel should be in physical contact with surface source at a higher temperature source (e.g. mantal, oil bath, steam bath etc.) Mechanism of heating involve conduction, and dielectric polarization, while Process of microwave synthesis is based on the principle where, in microwave oven the interaction of charged particle of the reaction material with electromagnetic wavelength of particular frequency takes place. The phenomena of producing heat by electromagnetic irradiation are ether by collision or by conduction, sometime by both. Mechanism in microwave oven involves the heating of material with use of high frequency electromagnetic waves.**

***Result:* The analgesic activity of the synthesized compounds (2A-2G) was evaluated by tail flick method, in which heat is used as a source to induce pain in mice. The increase in the reaction time (time interval) compared to basal is proportional to analgesic activity of the test compounds.**

***Keywords*: Analgesic activity, Green chemistry, Ibuprofen Xanthenedione derivatives.**

1. Introduction

Sustainable development and environmental issues are at the forefront of public and government concern. The ever increasing awareness of the need to protect natural resources through the development of environmentally sustainable processes and the optimization of energy consumption has guided the actions of both the private and governmental sectors of society. Since the late 90s of the 20th century, green chemistry research is strategy to eliminate pollution from the headstream of chemical process and provides a solution for environmental protection and sustainable development of society and economy. The term green chemistry was introduced as sustainable chemistry by a great scientist Paul Anastas (1). Green Chemistry is "The invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances". Definition of green chemistry is short but appears straight forward, it marks a significant departure in such a manner where the up-front design of the molecules and molecular transformations where the environmental issues have been considered or ignored as the heart of the chemical enterprise. This science of green chemistry mainly throw light on the intrinsic hazard of a chemical or chemical process. Green chemistry has received maximum attention (2-8) and from all over the world concept of green chemistry is used for creativity and innovation for the development of new synthetic methods, reaction conditions, analytical tools, catalysts. Various techniques are use in the green chemistry approach in order to synthesize the various products some are listed below.

- Solvent-free reactions
- Microwave assisted synthesis
- Ultrasound assisted synthesis
- Ionic liquids in organic synthesis
- Organic synthesis in water

Advantages of Solvent-free reactions (9):

- In this method use of volatile organic solvents is avoided.
- In this solvent-free reactions pollution is reduce and also the handling cost is also reduce due to over simplification of experimental procedures.
- In order to carry out the reaction thermal process or irradiation with UV, microwave or ultrasound can be employed.
- No need to recover, purify the solvent, reducing the pollution arising from such operations.

2. Montmorillonite (10,11)

A. Introduction

The montmorillonite is $(Na,Ca)_{0.3}$ $(Al,Mg)_2$ Si_4O_{10} $(OH)_2$. nH_2O and the theoretical composition without the interlayer

material is SiO_2: 66.7%, Al_2O_3: 28.3%, H_2O: 5%. Montmorillonite is expansible 2:1 phyllosilicate clay having permanent layer charge. The structure of montmorillonite consists of two silica tetrahedral sheets joined by a central alumina octahedral sheet. The common layer is formed by combining the tips of the tetrahedron of each silica and one of the hydroxyl layers of the octahedral sheet. Substitution of Fe^{3+}, Fe^{2+}, and Mg^{2+} for Al^{3+} in the octahedral sheet and substitution of silicon by aluminum in the tetrahedral sheets create charge imbalance. This is balanced by exchangeable cations adsorbed between the unit layers and on the edges. Substitution within the lattice causes about 80% and broken bonds around the edges of the particles, about 20% of the total cation exchange capacity of montmorillonite. Sodium montmorillonites have a c-axis spacing of about 12.3 Å and calcium montmorillonites have a c-axis spacing of about 15 Å.

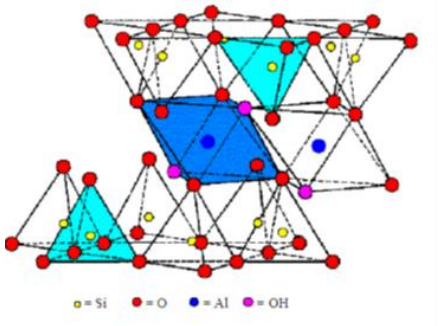


Fig. 1. Structure of Montmorillonite

Uses of montmorillonite: The physical and chemical properties of montmorillonite are very different from kaolinite. Due to these differences in the physical and chemical properties montmorillonite and other smectite clays have applications in many different areas. Some of such applications are:

a) Bentonite, whose primary constituent is sodium montmorillonite, is widely used as drilling fluid in petroleum exploration.

b) Sodium bentonite is used in pelletizing iron ore.

c) Montmorillonite is widely used as a catalyst and is considered as very promising in large number of organic synthesis and other reactions.

Recently, A synthesis of benzofluorenones by intra molecular cyclization of β-arylidene-β-benzoylpropionic acid andthe reaction was promoted proficiently b extremely small amounts of montmorilloniteK10 acting as a heterogeneous catalyst using ethanolic medium at 100^0C has been describe [(10)].

Clays and clay minerals (12-15):

Definition: A clay material is any natural, earthy, argillaceous material consisting of Extremely fine-grained minerals and colloidal substances (11). As a rock term, clay is the fraction of particle size less than 4 μ (12) which is used by engineers and soil scientists. The generally accepted upper limit of these hydrous alumino-silicate minerals is 2 μ. The term clay is used in reference to material that becomes plastic when mixed with a small amount of water (13,14). The Particle of clay minerals may be crystalline or amorphous, platy or fibrous and may vary from colloid dimensions to those above the limit of resolution of an ordinary microscope (15). The atomic structure of clay minerals has well defined crystal structure composed of two basic units, an octahedral sheet and a tetrahedral sheet (16). An octahedral sheet is usually composed of six oxygen atoms or hydroxyl groups around aluminum or some other cations arranged in octahedral coordination. When aluminium with a positive valence of 3 is the cation present in the octahedral sheet, only two-thirds of the possible positions are filled in order to balance the charges.

Kaolinite (17,18):

Structure of kaolinite

The theoretical chemical composition of kaolinite is SiO2: 46.54%; Al2O3: 39.50%; and H2O: 13.96% with the structural formula Al2Si2O5(OH)2. Kaolinite is a 1:1 clay consisting of a tetrahedral sheet and an octahedral sheet. The tips of the silica tetrahedral point towards the octahedral sheet forming a common layer of all the apical oxygen atoms (Fig. 1.7). Silicon and aluminum atoms share two-thirds of the O-atoms and the remaining one-third, which consists of hydroxyl groups, coordinated to the Al-atoms alone. Two-thirds of the octahedral positions are filled by aluminum atoms and one third remains vacant. Four oxygen atoms and eight hydroxyl groups surround the aluminum atoms.

Uses of kaolinite (19-22)

The physical and chemical properties of kaolinite make it useful in a number of industrial applications. Some of the important applications are:

1) Coating and filling of paper, due to coating paper sheet become smoother, brighter, glossier, more opaque, and most importantly, improves the printability Filling of paper with clay improves the brightness, opacity, smoothness, ink receptivity and printability.
2) Kaolinite is used as a pigment extender in water-based interior latex paints and in oil- based exterior industrial primers. It contributes suspension, viscosity and leveling of paints.
3) Kaolinite is widely used in the manufacture of ceramics due to its high refractory properties.

Every method which is used for synthesis of chemical compound has its own advantages.

Methods used for synthesizing the chemical moiety are

- Conventional method of synthesis of compounds.
- Microwave Method

In conventional method of synthesis of compound, the reaction mixture is heated and this heating proceeds a surface usually inside surface of reaction vessels. The vessel should be in physical contact with surface source at a higher temperature source (e.g. mantal, oil bath, steam bath etc.) By thermal or electric source heating take place. Mechanism of heating involve conduction, and dielectric polarisation. Heat transfer occurs from wall surface of vessel, to the mixture and

eventually to reacting species. In conventional heating, the highest temperature (for an open vessels) can be achieved and is limited by boiling point of particular mixture. On other hand Organic synthesis by microwave assisted method is emerged as a new "lead" in branch of chemistry. Microwave assisted synthesis is simple, clean, fast, efficient, and economic for the synthesis of a large number of organic molecules. Now day's technique is considered as an important approach toward green chemistry, because this technique is more environmentally friendly. This technology is still under-used in the laboratory and has the potential to have a large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development.

Microwave heating refers the use of electromagnetic waves ranges from 0.01m to 1m wave length of certain frequency to generate heat in the material. These microwaves lie in the region of the electromagnetic spectrum between millimeter wave and radio wave i.e. between I.R and radio wave.

Process of microwave synthesis is based on the principle where, in microwave oven the interaction of charged particle of the reaction material with electromagnetic wavelength of particular frequency takes place. The phenomena of producing heat by electromagnetic irradiation are ether by collision or by conduction, sometime by both. Mechanism in microwave oven involves the heating of material with use of high frequency electromagnetic waves. The interaction of electric field component of the wave with the charged particles in the material results in the heating. Inadequate controls in the rudimentary equipment employed, however, generated hazards, including explosions. In the electromagnetic radiation spectrum, microwaves (300 MHz–300000 MHz) lie between radio wave (RF) and infrared (IR) frequencies. This include the region that will affect molecular rotation, though the preferred frequency of 2450 MHz, chosen by microwave instrumentation manufacturers falls below any of the rotational transitions that will occur in molecules, one of the four available frequencies for industrial, scientific or medical applications, 2450 MHz is preferred because it has the right penetration depth to interact with laboratory scale samples and has become the standard for bench top systems. Microwaves, a non-ionizing radiation incapable of breaking bonds, are a form of energy and not heat and are manifested as heat through their interaction with the medium or materials wherein they can be reflected (metals), transmitted (good insulators that will not heat) or absorbed (decreasing the available microwave energy and rapidly heating the ample). Microwave reactions involve selective absorption of electromagnetic waves by polar molecules, non- polar molecules being inert to microwaves. When molecules with a permanent dipole are submitted to an electric field, they become aligned and as the field oscillates their orientation changes, this rapid reorientation produces intense internal heating.

Examples of the microwave assisted organic synthesis include synthesis of N-Phenyl ethyl benzene sulfonamide (3) by reacting 2-vinylbenzene (1) and benzenesulfonamide (2) under microwave irradiation was done (23) (1700C at a maximum of 60 W). Microwave irradiation is used to carry out organic reactions such as pericyclic, cyclization, aromatic substitution(27)., oxidation (28) alkylation(29) decarboxylation (30) radical reactions(31)condensation(32), peptide synthesis. (33).

The Microwave irradiation for the synthesis of substituted benzimidazoles in the presence of Montmorillonite K-10 has been carried out and their derivatives exhibited array of biological activities such as local anesthetic (34) antipyretic(35) and antihistaminic(36) hence holds a great chemotherapeutic potential(37).

3. Biological activity of heterocyclic compounds

A. A brief review

Heterocyclic chemistry is a very important branch of organic chemistry accounting for nearly one-third of modern publications. In fact, two-third of organic compounds is heterocyclic compounds. A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbocyclic compound. The heterocyclic compound is the compound which is aromatic and contains at least one hetero atom i.e. the atom other than the carbon in the ring. Generally, nitrogen, oxygen, sulphur are the most common heteroatoms. But the heterocyclic compounds containing other hetero atoms also exist. An enormous number of heterocyclic compounds are known and this number is increasing rapidly. As per the literature, the variety of heterocyclic compounds is enormous, their chemistry is complex and synthesizing them requires great skill. Among large number of heterocyclic compounds found in nature nitrogen containing heterocyclic compounds are most abundant than those containing oxygen or sulphur. Heterocyclic systems are encountered in many groups of organic compounds possessing great applicability in industry as well as in our life in various ways i. e. most of the sugars and their derivatives, including vitamin C, for instance, exist largely in the form of five membered or six membered ring containing one oxygen atom. Heterocyclic compounds containing nitrogen; are possessed by many members of vitamin B group. one example is vitamin B6 (Pyridoxine), which is a derivative of the pyridine, essential in amino acid metabolism. Natural products like alkaloids and glycosides have been used since old age, as remedial agents. The important examples of heterocyclic compounds are febrifugal alkaloid from ancient Chinese drug, Chang Shan, reserpine from Indian rawualfia, curen alkaloid from arrow poison, codenine, J-tropine and strychnine. Similarly, the antibiotics like penicillin, cephalosporin, norfloxacin, streptomycin etc. also contain heterocyclic ring systems. Majority of the large number of drugs being introduced in pharmacopeia's in recent years are heterocyclic compounds. Broad spectrum anthelminthic drug like pyrantel and morantel are the drug of choice. The herbicides atrazine and simazine are well known examples of heterocyclic agrochemicals. Plant pigments such as indigo, haemoglobin and

anthiocyanins, chlorophyll has contributed much to colour chemistry and many other heterocyclic colouring matters are in use since prehistoric times. Taking in view of the applicability of heterocyclic compounds, we have undertaken the synthesis of heterocycles bearing pyrazole, pyrans and Xanthenediaone.

B. Xanthenediaone

Xanthene derivatives due to their promising activity attracted scientists all over the world in the field of medicinal and material chemistry. Xanthenediaone play a vital role as the key structural unit in a variety of natural products showing several biological activities. Due to the presence of in-built pyran ring architecture and their extended conjugation with aromatic groups, Xanthenediaone exhibit applications in optoelectronic materials. They form an important component in laser dyes6 and are used in laser technologies for photodynamic therapy. Xanthenediaone are used as pH sensitive fluorescent materials for visualization of biomolecules. In view of this aspect the importance of Xanthenediaone, extend the conjugation within the Xanthenediaone moiety by replacing the simple/substituted phenyl groups with tricyclic heterocycles.

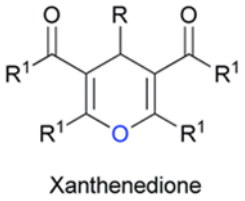


Fig. 2. Naturally occurring Xanthenediaone

C. Method

Microwave assisted multi-component synthesis of Xanthenediaone and their analogues

Innovative field of organic research is search for chemical structures which exhibit physiological activity. Observations of interesting biological activity of heterocyclic compounds is new pathway for the synthesis of new heterocycles. Chemically xanthene (9H-xanthene, 10H-9-oxaanthracene) is a yellow organic heterocyclic compound. Its chemical formula is $C_{13}H_{10}O$. It is soluble in diethyl ether. Its melting point is 101-102 °C and its boiling point is 310-312 °C. Xanthene is used as a fungicide and it is also a useful intermediate in organic synthesis. Derivatives of xanthene are commonly referred to collectively as xanthenes. Natural and synthetic xanthone derivatives are well-known for their ability to act as antioxidants and/or enzyme inhibitors. Among the various classes of natural compounds, xanthene derivatives have received special attention since many of these compounds have biological and therapeutic properties (40). Xanthene derivatives are recognized for their use as sensitizing dyes (41), in photodynamic therapy to destroy tumor cells (42)In laser technologies(43)and in pH-sensitive fluorescents materials for the visualization of biomolecules. Research has focused on secondary metabolites of the genus Allanblackia and the significant increase in the number of studies stems from the fact that many of these secondary metabolites, such as xanthene's, benzophenones and pentacyclic triterpenes, exhibit biological, pharmacological, anti-inflammatory, antimicrobial, antifungal, HIV-inhibitory and cytotoxic properties .The plants of the genus Allanblackia, which belong to the family Clusiaceae, are found inlarge forests in the west and south of the province of Cameroon, where they are used to treat respiratory diseases, toothache and diarrhoea Rhodomyrtone A drhodomyrtosone. I(II)extracted from Rhodomyr-tustomentosa together with the compound known as BF-6 (III) extracted from the leaves of Baeckea frutescensare examples of natural xanthenediones.

Xanthene derivatives can be prepared by several methods: cyclodehydration(44) the trapping of benzenes by phenols(45) the palladium-catalysed cyclisation of poly-cyclic aryltriflate esters(46), a simple and efficient procedure for the synthesis of xanthene derivatives through one-pot condensa-tion of 2-naphthol with aryl aldehydes in the pres-ence of niobium pentachloride(47).Present work deals with the synthesis of xanthenediones analogues from different aldehydes and finding out it's importance in biological system.

Xanthenedione derivatives were prepared through the condensation reaction of aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione promoted by acidic ionic liquid. The reaction time was 20–40 min with the yields between 82.3% and 95.3%. Also Xanthenedione derivatives were synthesized by one-pot reactions between aryl aldehyde derivatives and 1,3cyclohexanedione promoted by niobium penta chloride.

Similarly, the microwave method for synthesis of Xanthenediaone analogues is as follows.

All chemicals were procured from Aldrich (Sigma–Aldrich, St. Louis, MO, USA) Chemical Corporation and were used without further purification. STAR- CEM Corporation made microwave was used for the synthesis.1H and 13C NMR spectra were recorded by Bruker AVANCE III-NMR (500MHz for 1H and 125 MHz for 13C) instruments using DMSO-d6. Chemical shifts (δ) were reported in ppm downfield from internal Me_4Si standard. Reactions were monitored by thin layer chromatography (TLC), performed on silica gel glass plates containing 60GF-254, and visualization on TLC was achieved by UV light. Column chromatography was performed by Merck 60–120 mesh silica gel. Mass spectra were recorded in VARIAN 1200. Melting points were measured on a Buchi 510 apparatus in open capillary tubes and were approximate.

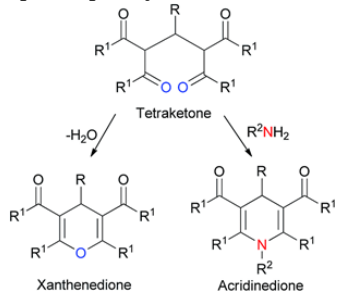


Fig. 3. Schematic presentation for general method of synthesis of xanthenediones

General Procedure for synthesis of 7-aryl-6H-benzo[h][1,3] dioxolo[4,5-b]xanthene-5,6(7H)-dione derivatives.

The reaction was carried out by microwave technique, in which a neat mixture of aromatic aldehydes (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (1.0 mmol) and 3,4-methylenedioxyphenol (1.0 mmol) and catalytic amount of Montmorillonite K10 (0.50 gm) in ethanol (4 ml) were added into a reaction tube and irradiated in a microwave reactor under continuous stirring in an open system under inert atmospheric pressure for the time mentioned in (Table 1). The reaction was monitored by TLC (petroleum ether/ethyl acetate Vol/Vol = 1/1). After completion of the reaction, the catalyst was filtered and washed with acetone several times. The filtrate was distilled off under vacuum and the residue was recrystallized from methanol to afford the product in excellent purity.

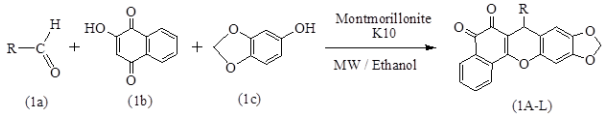


Fig. 4. Schematic representation synthesis of 7-aryl-6H-benzo[h][1,3] dioxolo[4,5-b]xanthene-5,6(7H)-dione derivatives.

Biological activity of Isolated compounds (analgesic)(55-57):

Biological activity of compound indicates its importance for curing the particular condition. Biological activity is of various type like antipyretic which covers the fever condition, anti-inflammatory and antipyretic which shows its effect against inflammation and against fever also. In addition to this biological activity of various compounds can determine in terms of analgesic activity, antifungal activity, antiseptic, antibacterial activity etc. An analgesic or painkiller is any member of the group of drugs used to achieve analgesia, relief from pain.

4. Result and discussion

To estimate the reaction condition, the reaction of 3,4-dimethoxybenzaldehyde (166.2 mg, 1.0 mmol), 3,4-methylenedioxyphenol (138.1 mg, 1.0 mmol), 2-hydroxy-1,4-naphthoquinone (174.1 mg, 1.0 mmol) in Ethanol (4.0mL) and MK10 (0.50gm) was selected as the model, the results are concise in (Table 1). Therefore, we selected 80^0C to study the effect of reaction time and found that 5 minutes is the optimum reaction time for the achievement of reactants into products.

Similarly, to find the estimate the quantity of scolecite, the above model reaction was carried out under the previously mentioned conditions, using different quantities of catalyst at 800C, the use of 0.50gm of catalyst resulted in the highest yield, 96% (Entry 4, Table 2).

MK10 results are far better than other reported catalysts in terms of yield as well and other reaction conditions (Table 3). To explore the opportunity of our methodology, extensive substituted new aromatic aldehydes were selected to synthesize innovative7-aryl-6H-benzo[h] [1,3] dioxolo [4,5-b] xanthene-5, 6 (7H)-dione derivatives, according to the investigational results as summarized in (Table 4).

Isolated yield; Reaction carried out at 80^0C; [c]Model reaction: 3,4-dimethoxybenzaldehyde (166.2 mg, 1.0 mmol), 3,4-methylenedioxyphenol (138.1 mg, 1.0 mmol), 2-hydroxy-1,4-naphthoquinone (174.1 mg, 1.0 mmol), solvents (4.0 mL).

[a]Isolated yield; [b]Model reaction:

3,4-dimethoxybenzaldehyde (166.2 mg, 1.0 mmol), 3,4-methylenedioxyphenol (138.1 mg, 1.0 mmol), 2-hydroxy-1,4-naphthoquinone (174.1 mg, 1.0 mmol), solvents (4.0 mL).

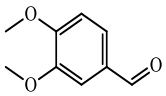
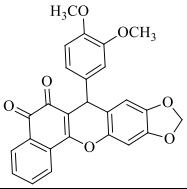
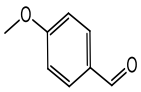
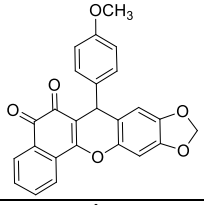
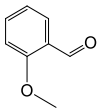
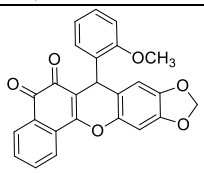
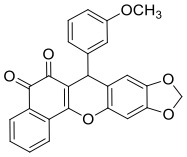
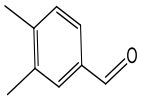
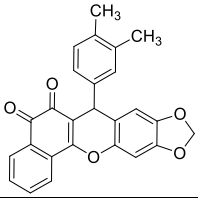
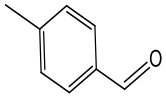
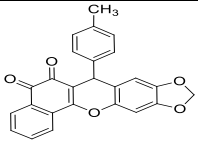
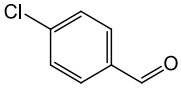
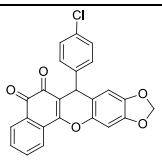
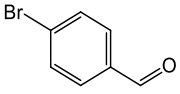
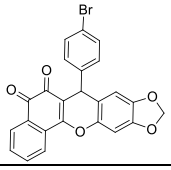
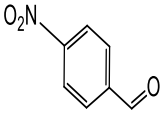
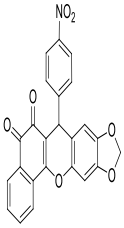
Table 1
Optimization of reaction conditions for synthesis of model product 1A

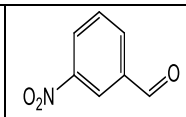
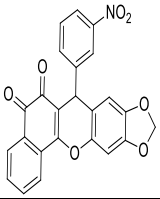
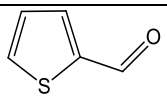
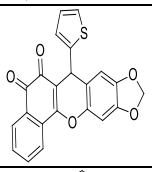
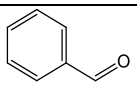
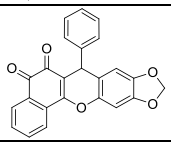
Entry	Solvent	Catalyst (mg)	Time (min)	Yield (%)[a,b]
1	Acetone	0.50	40	35
2	Toluene	0.50	50	38
3	Chloroform	0.50	35	55
4	Acetonitrile	0.50	10	81
5	Methanol	0.50	10	78
6	Ethanol	0.35	05	90
7	Ethanol	0.45	05	91
8	**Ethanol**	**0.50**	**05**	**94**

Table 2
Comparison results of other reported procedures with the present method in terms of time and yield

Entry	Solvents	Catalyst (mol %)	Time (min)	Temp. (^{0}C)	Yield (%)
1	Ethanol	Et_3N (20)	180	80	Very trace
2	Ethanol	Piperidine (20)	180	80	Trace
3	Ethanol	$MgCl_2$ (20)	90	80	81
4	Ethanol	$InCl_3$ (20)	120	80	72
5	Ethanol	$NiCl_3.6H_2O$ (20)	90	80	80
6	Ethanol	$Zn(OTf)_2$ (20)	90	80	84
7	Ethanol	CSA (20)	90	80	81
8	Ethanol	CH_3COOH (20)	120	80	68
9	Ethanol	NH_2SO_3H (20)	120	80	76
10	Ethanol	P-TSA (20)	40	100	93
11	**Ethanol**	**MK 10**	**3 (MW)**	**70**	**94 (Present work)**

Table 3
Synthesis of 7-aryl-6H-benzo[h][1,3]dioxolo[4,5-b]xanthene-5,6(7H)-dione derivative.

Product	Aldehyde	Product	Time (min)	Yield (%)[x]	MP (^{0}C)
1A			4	94	235-237[236] [a]
1B			4	90	235-237 [234][a]
1C			4	88	233-234 [234][a]
1D			4	91	223-225 [225][a]
1E			4	88	236-238 [236][a]
1F			4	92	232-235 [231][a]
1G			4	88	239-240 [240][a]
1H			4	87	252-254 [251][a]
1I			4	84	220-221 [221][a]

1J			4	86	240-243 [242][a]
1K			4	88	224-226 [225][a]
1L			4	91	252-253 [253][a]

Yields refer to those of pure isolated products characterized by 1H &13C NMR, Mass spectra.
NIL- Product not recovered)

Table 4
Recycling of MK 10(0.50 gm) for the synthesis of model product 1A

Sr. no.	Cycle	Yield (%)
1	Fresh	94
2	1st	88
3	2nd	80
4	3rd	73

5. Result of analgesic activity of synthesized xanthenedione analogues

Biological activity of compound indicates its importance for curing the particular condition. Biological activity is of various type like antipyretic which covers the fever condition, anti-inflammatory and antipyretic which shows its effect against inflammation and against fever also. In addition to this biological activity of various compounds can determine in terms of analgesic activity, antifungal activity, antiseptic, antibacterial activity etc.

An analgesic or painkiller is any member of the group of drugs used to achieve analgesia, relief from pain. Analgesic drugs act in various ways on the peripheral and central nervous systems.

They are distinct from anesthetics, which temporarily affect, and in some instances completely eliminate, sensation.

6. Classification of analgesics (58-63)

Analgesics are typically classified based on their mechanism of action.

A. Paracetamol (acetaminophen)

Main article: Paracetamol: Paracetamol, also known as acetaminophen or APAP, is a medication used to treat pain and fever. It is typically used for mild to moderate pain. In combination with opioid pain medication, paracetamol is used for more severe pain such as cancer pain and after surgery. It is typically used either by mouth or rectally but is also available intravenously. Effects last between two and four hours. Paracetamol is classified as a mild analgesic. Paracetamol is generally safe at recommended doses.

B. NSAIDs

Nonsteroidal anti-inflammatory drugs (usually abbreviated to NSAIDs), are a drug class that groups together drugs that decrease pain and lower fever, and, in higher doses decrease inflammation. The most prominent members of this group of drugs, aspirin, ibuprofen and naproxen, are all available over the counter in most countries.COX-2 inhibitors These drugs have been derived from NSAIDs. The cyclooxygenase enzyme inhibited by NSAIDs was discovered to have at least 2 different versions: COX1 and COX2. Research suggested most of the adverse effects of NSAIDs to be mediated by blocking the COX1 (constitutive) enzyme, with the analgesic effects being mediated by the COX2 (inducible) enzyme. Thus, the COX2 inhibitors were developed to inhibit only the COX2 enzyme (traditional NSAIDs block both versions in general). These drugs (such as rofecoxib, celecoxib, and etoricoxib) are equally effective analgesics when compared with NSAIDs, but cause less gastrointestinal hemorrhage in particular.

C. Opioids

Morphine, the archetypal opioid, and other opioids (e.g., codeine, oxycodone, hydrocodone, dihydromorphine, pethidine) all exert a similar influence on the cerebralopioid receptor system. Buprenorphine is a partial agonist of the μ-opioid receptor, and tramadol is a serotonin norepinephrine reuptake inhibitor (SNRI) with weak μ-opioid receptor agonist properties. Tramadol is structurally closer to venlafaxine than to codeine and delivers analgesia by not only delivering "opioid-like" effects (through mild agonism of the mu receptor) but also by acting as a weak but fast-acting serotonin releasing agent and norepinephrine reuptake inhibitor. Tapentadol, with some structural similarities to tramadol, presents what is believed to be a novel drug working through two (and possibly three) different modes of action in the fashion of both a traditional opioid and as a SNRI. The effects of serotonin and norepinephrine on pain, while not completely understood, have

had causal links established and drugs in the SNRI class are commonly used in conjunction with opioids (especially tapentadol and tramadol) with greater success in pain relief. Patients starting morphine may experience nausea and vomiting (generally relieved by a short course of antiemetics such as phenergan). Pruritus (itching) may require switching to a different opioid. Constipation occurs in almost all patients on opioids, and laxatives (lactulose, macrogol-containing or co-danthramer) are typically co-prescribed.

Alcohol Describing the effects of using alcohol to treat pain is difficult. Alcohol has biological, mental, and social effects which influence the consequences of using alcohol for pain. Moderate use of alcohol can lessen certain types of pain in certain circumstances. Attempting to use alcohol to treat pain has also been observed to lead to negative outcomes including excessive drinking and alcohol use disorder.

D. Medical cannabis

Medical cannabis or medical marijuana, can refer to the use of cannabis and its cannabinoids to treat disease or improve symptoms. There is evidence suggesting that cannabis can be used to treat chronic pain and muscle spasms; with some trials indicating improved relief of neuropathic pain over opioids.

E. Combinations

Analgesics are frequently used in combination, such as the paracetamol and codeine preparations found in many non-prescription pain relievers. They can also be found in combination with vasoconstrictor drugs such as pseudoephedrine for sinus-related preparations, or with antihistamine drugs for allergy sufferers.

Psychotropic agent's Other psychotropic analgesic agents include ketamine (an NMDA receptor antagonist), clonidine and other α2-adrenoreceptor agonists, and mexiletine and other local anaesthetic analogues. Other drugs Drugs that have been introduced for uses other than analgesics are also used in pain management. Both first-generation (such as amitriptyline) and newer anti-depressants (such as duloxetine) are used alongside NSAIDs and opioids for pain involving nerve damage and similar problems. Other agents directly potentiate the effects of analgesics, such as using hydroxyzine, promethazine, carisoprodol, or tripelennamine to increase the pain-killing ability of a given dose of opioid analgesic. Adjuvant analgesics, also called atypical analgesics, include nefopam, orphenadrine, pregabalin, gabapentin, cyclobenzaprine, hyoscine (scopolamine), and other drugs possessing anticonvulsant, anticholinergic, and/or antispasmodic properties, as well as many other drugs with CNS actions. These drugs are used along with analgesics to modulate and/or modify the action of opioids when used against pain, especially of neuropathic origin.

F. Other uses

Topical analgesia is generally recommended to avoid systemic side-effects. Painful joints, for example, may be treated with an ibuprofen- or diclofenac-containing gel (The labeling for topical diclofenac has been updated to warn about drug-induced hepatotoxicity. capsaicin also is used topically. Lidocaine, an anesthetic, and steroids may be injected into painful joints for longer-term pain relief. Lidocaine is also used for painful mouth sores and to numb areas for dental work and minor medical procedures. In February 2007 the FDA notified consumers and healthcare professionals of the potential hazards of topical anesthetics entering the blood stream when applied in large doses to the skin without medical supervision. These topical anesthetics contain anesthetic drugs such as lidocaine, tetracaine, benzocaine, and prilocaine in a cream, ointment, or gel.

7. Analgesic activity of Xanthenediaoneanalogues

Biological Activity (64-73). In the present investigation, evaluation of analgesic activities of newly synthesized compounds were carried out by the following in vivo method.

8. Experimental section

A. Materials and Methods

All chemicals and reagents were purchased from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) or Spectrochem Pvt. Ltd (Mumbai, India) and were used without further purification. All the slandered drugs like Ibuprofen, Dr. Reddy's lab, were purchased from the local Pharmacy, Nagpur (Maharashtra).

B. In vivo pharmacology

Tail flick (tail-withdrawal from the radiant heat) method was conducted according to D'Amour et al using an analgesiometer was adopted for evaluation of analgesic activity of the test compounds and standard. Basal reaction time has been taken to radiant heat by placing the tip (last 1-2 cm) of the tail of the animals (control, standard and test groups) individually. The tail-withdrawal from the heat is taken as the end point. Ibuprofen and test compounds were suspended in sodium CMC (1% W/V) aqueous suspension. Albino mice of either sex (20-25 gm) were divided into twelve groups of six animals each and they were numbered individually. All groups were fasted for 24 hour before administering the drug with water ad libitum. Group-1 was administered with only 1% w/v sodium CMC suspension (1 ml/kg, p.o.) which served as control. Group-2 was administered with ibuprofen (10 mg/kg, p.o.) which served as a standard. Group-3 to 12 (10 mg/kg, p.o.) were administered with test compounds respectively. All the animals were held in position by a suitable restrained with the tail extending out. The time in seconds taken to withdraw the tail as the reaction time and was recorded at 0, 0.5, 1, 2 and 4 h after administration of compounds. A cut off point of 10 sec was observed to prevent the tail damage. The percentage of protection in the control, standard drug and compound treated animals were calculated. The results and statistical analysis of analgesic activity of control, ibuprofen and the compounds tested are shown in table.

Table 5
Analgesic activity of synthesized compounds (1A-1L)

Sr. no.	Synthetic Compounds	% inhibition ± SEM at various time intervals			
		0.5 hour	1 hour	2 hour	4 hour
1.	Ibuprofen	55.26 ± 0.90*	89.95 ± 0.97*	99.87 ± 1.86*	58.02 ± 2.22*
2.	1A	50.56 ± 0.59*	83.59 ± 1.73*	90.04 ± 1.39*	57.69 ± 0.59
3.	1B	28.35 ± 1.34	47.21 ± 1.68	69.39 ± 2.71	34.28 ± 1.41
4.	1C	40.64 ± 1.38	73.76 ± 1.68	80.84 ± 1.42	30.25 ± 1.48
5.	1D	42.67 ± 2.86	77.81 ± 1.97*	83.35 ± 1.86	34.34 ± 1.81
6.	1E	24.75 ± 0.86	80.73 ± 1.29*	87.47 ± 1.47*	30.73 ± 1.09
7.	1F	40.22 ± 1.75	70.37 ± 2.73*	82.46 ± 1.82	42.34 ± 2.12
8.	1G	53.73 ± 1.73*	88.27 ± 1.83*	92.34 ± 1.32*	58.31 ± 1.52
9	1H	55.73 ± 1.80*	90.27 ± 1.85*	94.34 ± 1.35*	60.31 ± 1.67
10	1I	57.83 ± 1.83*	92.72 ± 1.88*	95.35 ± 1.37*	63.32 ± 1.69
11	1J	60.33 ± 2.34*	95.78 ± 2.01*	97.37 ± 2.30*	67.38 ± 2.75
12	1K	66.45 ± 3.74*	97.87 ± 2.34*	98.43 ± 2.78*	70.31 ± 3.01
13	1L	69.75 ± 4.07*	98.88 ± 3.01*	99.67 ± 2.89*	71.54 ± 3.89

Table 5, showing analgesic activity results of isolated Xanthenediaone derivatives.
All values are represented as mean ± S.E.M. (n = 6).
$p<0.01$ compared to control group. One-way ANOVA, Dennett's t-test
Dosage: Ibuprofen-10 mg/kg and test compounds- 10mg/kg body weight orally.

9. Conclusion

The analgesic activity of the synthesized compounds (2A-2G) was evaluated by tail flick method, in which heat is used as a source to induce pain in mice. The increase in the reaction time (time interval) compared to basal is proportional to analgesic activity of the test compounds. The results are summarized in table.

Compounds (2A-2G) showed dose dependent activity with higher protection at 120 min which is comparable to the reference standard and exerted their activity in a manner similar to that of the well-established drug Ibuprofen because they carry methylenedioxy benzene nucleus and naphthoquinone at aromatic pyran ring the dimethoxy substituent was present which is attached to nucleus (2A). In addition, it was found that the compounds having methyl substituents (2E) and nitro group present at (5I) substituents present in other compounds in nucleus exhibited moderate analgesic activity and the activity has been increased at 60 min and reached to the maximum at 120 min. Among all, compound (2A) was found to exhibit significant analgesic activity at 120 min. These results indicated that (2F) and (2G) are more promising molecules as analgesic agents respectively and further studies are required to elucidation of exact mechanism of action for their therapeutic potential.

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