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SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL CHALCONES WITH METHANE-SULFONYL END AS POTENT ANALGESIC AND ANTI-INFLAMMATORY AGENTS

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Keywords:

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ABSTRACT: In the present study, eleven new chalcones bearing a methanesulfonyl group at *para* position have been synthesized by the condensation of 4-methylsulphonylacetophenone with different *para*-substituted aromatic aldehydes. The structures of the newly synthesized molecules were elucidated by spectroscopic methods such as as ^{1}H NMR, ^{13}C NMR, and mass. These compounds were screened for their anti-inflammatory activity by carrageenan-induced rat paw edema and leucocytes migration methods and analgesic activity by acetic acid-induced writhing test in albino Wistar rats. Among the synthesized compounds, MS7 to MS10 which contain electron-withdrawing groups were found to be most active with reference to anti-inflammatory activity at a dose level of 10 mg/kg and caused a significant reduction in the number of recruited leukocytes and inhibition of pleural exudates formation that was comparable to that of indomethacin at a dose of 10 mg/kg. The compounds which contain halogens and methoxy groups showed a significant analgesic activity at a dose of 10 mg/kg when compared to standard diclofenac sodium. Thus, it can be concluded that among the compounds tested, the ones with halogens possess significant anti-inflammatory and analgesic activity in rats. Further studies involving the investigations of the biochemical pathways may result in the identification of lead with potent anti-inflammatory and analgesic activity and with low toxicity and better therapeutic index.

INTRODUCTION: Inflammation is a pathological process whereby the human body responds or reacts to an injury of any sort like physical injury, an infection, or inappropriate stimulation of the immune system. One of the major responses is through the vascular system wherein the leucocytes are attracted to the site of injury by chemotaxis. This subsequently results in tissue damage by the release of proteolytic enzymes. Pain, which is one of the cardinal signs of inflammation, is due to the stimulation of nociceptors that detect signals from damaged peripheral tissue. Noxious chemicals like bradykinin, histamine, and 5-HT are released in the injured tissues during inflammation. The prostaglandins, which are the major cause for inflammation, do not directly produce pain but appear to sensitize the nociception to these chemicals. Hence inhibition of prostaglandins synthesis forms the rationale for design anti-inflammatory drugs [1].

A variety of synthetic compounds have proved to be useful in animal models for inflammation [2-5].

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Many synthetic compounds containing chalcones play a key role in the drug design and development of new chemical entities. These chalcones and their derivatives exhibit many promising pharmaceutical applications, including analgesic and anti-inflammatory activities [6-20]. Though many of the anti-inflammatory drugs that are currently available in the market reduce the major symptoms of inflammation like redness, swelling, heat, and pain, still research goes on in search of better anti-inflammatory agents with the less toxic profile. Gastric disturbances are the major problem with these agents, which is due to inhibition of the synthesis of mucoprotective prostaglandins along with the prostaglandins, which are responsible for inflammations [21].

With this background, the present study was undertaken to synthesize novel chalcones with methanesulfonyl group at *para* position in ring A and different *para*-substituted groups on ring B and screened for analgesic and anti-inflammatory activities as the initial step of the search for better agents.

MATERIALS AND METHODS:

Chemicals and Reagents: All chemicals and reagents used in this study were of analytical grade. Carrageenan and other chemicals used for this study were purchased from a Sigma-Aldrich chemical company. Indomethacin was procured as marketed formulation from Sun Pharmaceuticals, Mumbai, India.

General Procedure for Synthesis of Methanesulfonyl Chalcones: Different *para* substituted benzaldehyde and 4-methylsulphonyl-acetophenone were dissolved as equimolar quantity in 40% w/v sodium hydroxide with ethanol as medium. The reaction mixture was stirred for 4 - 6 h and then poured into ice-cold water. The precipitated product was washed using water, dried, and recrystallized from ethanol. All the newly synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy and summarized below.

(2*E*)- 1- [4-(methanesulfonyl)phenyl]- 3- phenyl prop-2-en-1-one (MS1): Pale yellow; Yield: 55.9%; m.p: 160-163°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.45 (s, 3H, $-SO_2CH_3$), 7.64-7.60 (1H, d, *J*= 16.0 Hz, $-CH_\alpha$), 6.94-785 (9H, ArH), 8.04-8.00 (d, *J*= 16.0 Hz, $-CH_ß$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 47.7, 121.3, 127.9, 128.6, 130.9, 135.2, 142.9, 146.8, 145.1, 189.7. ESI-MS (*m/z*): Calculated- 286.35, Observed- 286.34.

(2*E*)-1-[4-(methanesulfonyl) phenyl]-3-(4-metho-xyphenyl)prop-2-en-1-one (MS2): Yellow; Yield: 74.3%; m.p: 181-183°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.41 (s, 3H, $-SO_2CH_3$), 3.59 (s, 3H, OCH_3), 7.66-7.62 (1H, d, *J*= 16.0 Hz, $-CH_\alpha$), 6.99-780 (8H, ArH), 8.05-8.01 (d, *J*= 16.0 Hz, $-CH_ß$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 47.70, 55.8, 114.2, 121.3, 127.5, 128.8, 130.2, 130.9, 142.9, 145.1, 146.8, 159.8, 189.7.ESI-MS (*m/z*): Calculated- 316.37, Observed- 316.36.

(2*E*)-1-[4-(methanesulfonyl) phenyl]-3-(4-methyl phenyl)prop-2-en-1-one (MS3): Pale white; Yield: 89.9%; m.p: 190-192°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.42 (s, 3H, $-SO_2CH_3$), 3.52 (s, 3H, CH_3), 7.65-7.61(1H, d, *J*= 16.0 Hz, $-CH_\alpha$), 7.00-789 (8H, ArH), 8.06-8.02 (d, *J*= 16.0 Hz, $-CH_ß$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.3, 47.7, 121.3, 128.5, 128.8, 130.9, 132.2, 137.6, 142.9, 145.1, 146.7, 189.8. ESI-MS (*m/z*): Calculated- 300.37, Observed- 300.36.

(2*E*)- 3- (4-ethylphenyl)- 1- [4-(methanesulfonyl) phenyl] prop-2-en-1-one (MS4): Pale white; Yield: 60.5%; m.p: 210-212°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27-1.24 (t, 3H, *J*= 8.0 Hz, CH_3-CH_2), 1.47-1.43, 3.42 (s, 3H, $-SO_2CH_3$), 7.68-7.64 (1H, d, *J*= 16.0 Hz, $-CH_\alpha$), 7.01-789 (8H, ArH), 8.02-7.98 (d, *J*= 16.0 Hz, $-CH_ß$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.50, 28.20, 47.6, 121.3, 127.6, 128.5, 128.8, 130.9, 132.4, 137.6, 142.9, 145.1, 145.3, 146.8, 189.7. ESI-MS (*m/z*): Calculated- 314.39, Observed- 314.38.

(2*E*)- 3- [4- (dimethylamino) phenyl] -1 - [4-(methanesulfonyl)phenyl]prop-2-en-1-one (MS5): Red; Yield: 75.9%; m.p: 151-153°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.02 (s, 6H, $N(CH_3)_2$), 3.43 (s, 3H, $-SO_2CH_3$), 7.64-7.60(1H, d, *J*= 16.0 Hz, $-CH_\alpha$), 6.99-785 (8H, ArH), 8.09-8.05 (d, *J*= 16.0 Hz, $-CH_ß$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 41.3, 47.7, 111.7, 121.3, 124.7, 128.8, 129.7, 130.9, 142.9, 145.1, 146.8, 150.3, 189.7. ESI-MS (*m/z*): Calculated- 329.41, Observed- 329.40.

(2*E*)-1-[4-(methanesulfonyl) phenyl]-3-(4-nitro-phenyl) prop-2-en-1-one (MS6): Brown; Yield: 36.3%; m.p: 172-174°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.43 (s, 3H, $-SO_2CH_3$), 7.64-7.60(1H, d, *J*= 16.0 Hz, $-CH_\alpha$), 6.99-789 (9H, ArH), 8.05-8.01 (d, *J*= 16.0 Hz, $-CH_ß$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: δ: 47.7, 121.3, 123.8, 128.9, 129.0, 130.9, 141.3, 142.9, 145.1, 146.8, 147.1, 189.7. ESI-MS (*m/z*): Calculated- 331.34, Observed- 331.39.

(2*E*)- 3- (4-chlorophenyl)-1-[4-(methanesulfonyl) phenyl]prop-2-en-1-one (MS7): Light brown; Yield: 84.5%; m.p: 179-181°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: ^{1}H NMR (400 MHz, $CDCl_3$)δ: 3.49 (s, 3H, $-SO_2CH_3$), 7.69-7.65 (1H, d, *J*= 16.0 Hz, $-CH_\alpha$), 6.93-7.97 (9H, ArH), 8.08-8.04 (d, *J*= 16.0 Hz, $-CH_ß$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 47.7, 121.3, 128.7, 128.8, 129.0, 130.9, 133.3, 133.5, 142.9, 145.1, 146.8, 189.7. ESI-MS (*m/z*): Calculated- 320.79, Observed- 320.78.

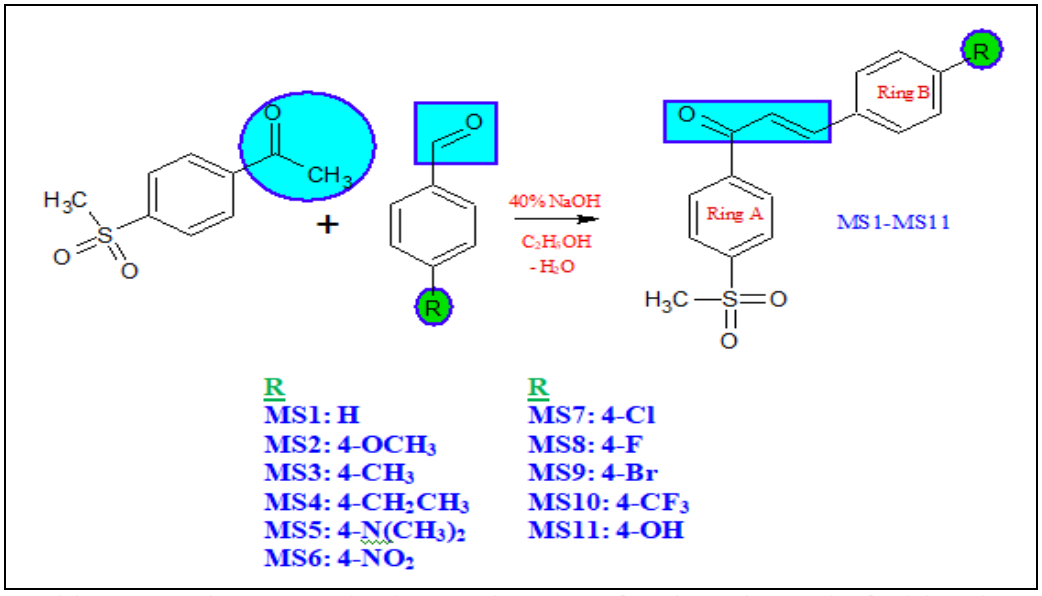
(2*E*)- 3- (4-fluorophenyl)-1-[4-(methanesulfonyl) phenyl]prop- 2- en- 1- one (MS8): Pale yellow; Yield: 82.2%; m.p: 164-166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.46 (s, 3H, $-SO_2CH_3$), 7.64-7.60(1H, d, *J*= 16.0 Hz, $-CH_\alpha$), 6.92-783 (9H, ArH), 8.05-8.01 (d, *J*= 16.0 Hz, $-CH_ß$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 47.7, 115.4, 121.3, 128.8, 130.4, 130.8, 130.9, 142.9, 145.1, 146.8, 162.1, 189.7. ESI-MS (*m/z*): Calculated- 304.34, Observed- 304.33.

(2*E*)- 3- (4-bromophenyl)-1-[4-(methanesulfonyl) phenyl] prop-2-en-1-one (MS9): Pale brown; Yield: 70.1%; m.p: 141-143°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.41 (s, 3H, $-SO_2CH_3$), 7.68-7.64 (1H, d, *J*= 16.0 Hz, $-CH_\alpha$), 6.91-7.88 (9H, ArH), 8.08-8.04 (d, *J*= 16.0 Hz, $-CH_ß$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 47.7, 121.3, 122.3, 128.6, 128.8, 130.9, 131.5, 134.2, 142.9, 145.1, 146.8, 189.7. ESI-MS (*m/z*): Calculated- 365.24, Observed- 365.23.

(2*E*)- 1- [4- (methanesulfonyl) phenyl]- 3- [4-(trifluoromethyl)phenyl]prop-2-en-1-one (MS10): Yellow; Yield: 81.2%; m.p: 183-184°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.40 (s, 3H, $-SO_2CH_3$), 7.64-7.60 (1H, d, *J*= 16.0 Hz, $-CH_\alpha$), 6.96-7.97 (9H, ArH), 8.09-8.05 (d, *J*= 16.0 Hz, $-CH_ß$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 47.7, 121.3, 124.1, 125.0, 128.8, 128.9, 130.2, 130.9, 138.5, 142.9, 145.1, 146.8, 189.7. ESI-MS (*m/z*): Calculated- 354.34, Observed-354.33.

(2*E*)- 3- (4- hydroxyphenyl)- 1- [4-(methane-sulfonyl) phenyl]prop-2-en-1-one (MS11): Light brown; Yield: 72.4%; m.p: 128-131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.43 (s, 3H, $-SO_2CH_3$), 5.89 (s, 1H, Ar-OH), 7.68-7.64 (1H, d, *J*= 16.0 Hz, $-CH_\alpha$), 7.00-786 (9H, ArH), 8.06-8.02 (d, *J*= 16.0 Hz, $-CH_ß$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 47.7, 115.8, 121.3, 127.8, 128.8, 130.6, 130.9, 142.9, 145.1, 146.8, 157.7, 189.7. ESI-MS (*m/z*): Calculated- 302.34, Observed- 302.33.

The synthetic route for the preparation of chalcones with methanesulfonyl end is outlined in **Scheme 1.**



SCHEME 1: SYNTHETIC ROUTE FOR METHANESULFONYL CHALCONES

All the synthesized compounds were characterized by their physical properties, and they are given in **Table 1.**

TABLE 1: PHYSICAL CHARACTERIZATION OF SYNTHESIZED COMPOUNDS

Compounds	R	Mol. Formula	Mol. weight	% Yield
MS1	H	$C_{16}H_{14}O_3S$	286.35	55.9
MS2	OCH_3	$C_{17}H_{16}O_4S$	316.37	74.3
MS3	CH_3	$C_{17}H_{16}O_3S$	300.37	89.9
MS4	CH_2CH_3	$C_{18}H_{18}O_3S$	314.39	60.5
MS5	$N(CH_3)_2$	$C_{18}H_{19}NO_3S$	329.41	75.9
MS6	NO_2	$C_{16}H_{13}NO_5S$	331.34	36.3
MS7	Cl	$C_{16}H_{13}ClO_3S$	320.79	84.5
MS8	F	$C_{16}H_{13}FO_3S$	304.34	82.2
MS9	Br	$C_{16}H_{13}BrO_3S$	365.24	70.1
MS10	CF_3	$C_{17}H_{13}F_3O_3S$	354.34	81.2
MS11	OH	$C_{16}H_{14}O_4S$	302.34	72.4

Anti-Inflammatory Activity:

Animals: Male albino Wistar rats (180 ± 5 g) were obtained from animal house, K.M. College of Pharmacy, Madurai, and maintained in standard laboratory conditions. They were given standard laboratory diet and water *ad libitum*. All animal experiments are approved by the Institutional animal ethics committee (IAEC/AU/Ph.D/KMCP/ 72/2019), and were in accordance with the guidelines of the Committee for the purpose of control and supervision of experiments on animal (CPCSEA), Government of India.

Acute Toxicity Evaluation: The acute toxicity of compounds was performed according to OECD-423 guidelines [2] on overnight-fasted albino Wistar rats (130 - 170 g) of either sex, and they were divided randomly into 14 groups of six animals each. The synthesized compounds were administered orally to the respective groups in increasing doses from 5, 50. 300 and 2000 mg/kg b.w, and the incidence of mortality were observed for three days. From the study, it was observed that there were no signs and symptoms of acute toxicity at the doses used.

Carrageenan-Induced Acute Inflammation in Rats: The anti-inflammatory activity of the various synthetic drugs was evaluated by carrageenan-induced rat paw edema method as per Pradeep *et al.*, 2015 with small modification [2] and it is used widely as a working model of inflammation in the search for new anti-inflammatory drugs. Albino Wistar rats (180 ± 5 g) were divided into 14 groups of 6 animals each and received tests/standard as given below.

Group I: Served as normal control (0.9% normal saline, I.P)

Group II: Served as a toxic control (0.1 ml of 1% w/v carrageenan in the subplantar region of the right hind paw).

Group III: Served as a standard which received indomethacin (10 mg/kg, b.w. I.P).

Group IV to XIV: Received MS1 to MS11 (10mg/kg, I.P)

Acute paw edema was induced in group II to XIV by injecting 0.1 ml of 1% w/v carrageenan solution, prepared in normal saline in the sub plantar region of the right hind paw. The change in paw volume was measured at 0 min, 30 min, 1h and 2h using a plethysmometer, and compared with that of the standard. The percentage of anti-inflammatory activity was calculated by using the formula:

$$\% \text{ Inhibition of edema} = (T - To) \times 100 / T$$

T - Thickness of paw in the control group; To, Thickness of paw edema in the test/standard compound treated group.

Carrageenan-Induced Pleurisy in Rats: The animals were divided into fourteen groups of six rats each as described in the carrageenan-induced paw edema model [22, 23,] and each was pre-treated with synthetic drugs at a dose of 10mg/kg I.P and indomethacin (10 mg/kg, I.P). One hour later, all the animals received 0.25 ml of an intrapleural injection of 1% w/v carrageenan on the right side of the thorax. The animals were sacrificed 3 h after carrageenan injection by ether inhalation. One ml of heparinized Hank's solution was injected into the pleural cavity and gently massaged to mix its contents. The fluid was aspirated out of the cavity, and the exudates were collected. The number of migrating leukocytes in the exudates was determined with Neubauer chamber. The values of each experimental group were expressed as mean ± SEM and compared with the toxic control group.

Analgesic Activity by Acetic Acid-Induced Writhing Test: The analgesic activity of the compounds was performed *in-vivo* by acetic-acid

writhing test [24] on male albino rats (180-220 g). Animals were divided into 13 groups (n = 6). Group 1 was kept as toxic control and treated with distilled water (1 ml). Animals of Groups 2 to 13 were administered orally with diclofenac and synthetic drugs (MS1 to MS11) (10 mg/kg b.w), respectively.

After 30 min, the animals of all the 13 groups were administered with I.P injection of 0.1 ml acetic acid (0.6%). Then, the count of abdominal contractions of animals during 30 min after acetic acid injection was reported, and the percentage analgesic activity (PAA) was calculated by using the following formula:

$$PAA = (C- CD) \times 100 / CD$$

C = Mean of contractions count in animals treated with various synthetic drugs and indomethacin. CD = Mean of contractions count in animals served as a negative control

Statistical Analysis: The results are reported as mean ± SEM. The statistical analyses were performed using one-way analysis of variance (ANOVA) followed by Tukey's test. For all tests, differences with values of P<0.01 were considered significant.

RESULTS AND DISCUSSION:

Anti-inflammatory Activity: Due to the increasing frequency of intake of NSAID's and their reported common side effects, there is a need to focus on the scientific exploration of various synthetic drugs having fewer side effects. So, there is a continuous search for indigenous drugs, which can provide relief to inflammation with minimal side effects. Compounds with sulfur-based functional groups have been proved successfully as anti-inflammatory drugs. Many marketed drugs, celecoxib, valdecoxib, meloxicam, piroxicam, tenoxicam, and nimesulide, which contain sulfur in their structure, were proved for their pharmacological activities [25].

Hence, we synthesized sulfur-based chalcones with different substituting groups at the para position in ring B and evaluated their anti-inflammatory activities by carrageenan-induced edema in rats, and results are given in **Table 2,** and the percentage inhibition of rat paw volume of various synthetic compounds is given in **Table 3.**

TABLE 2: RESULTS OF MEAN INCREASE IN PAW VOLUME OF METHANESULFONYL CHALCONES IN CARRAGEENAN INDUCED RAT PAW EDEMA MODEL

Treatment	Mean paw volume before carrageenan injection	Mean increase in paw volume after carrageenan injection (ml)		
	0 min	30min	1h	2h
Normal	0.90 ± 0.06	0.90 ± 0.52	0.91 ± 0.26	0.90 ± 0.31
Toxic	0.91 ± 0.82	1.89 ± 0.41^{*a}	3.42 ± 0.26^{*a}	3.02 ± 0.13^{*a}
Standard	0.89 ± 0.10	1.09 ± 0.23^{ns}	1.30 ± 0.10^{*b}	1.21 ± 0.16^{*b}
MS1	0.91 ± 0.23	1.62 ± 0.26^{ns}	2.42 ± 0.34^{ns}	2.37 ± 0.35^{ns}
MS2	0.92 ± 0.34	1.15 ± 0.17^{ns}	1.45 ± 0.18^{*b}	1.66 ± 0.11^{*b}
MS3	1.02 ± 0.31	1.56 ± 0.26^{ns}	2.05 ± 0.16^{*b}	2.02 ± 0.16^{*b}
MS4	0.89 ± 0.23	1.39 ± 0.12^{ns}	1.96 ± 0.12^{*b}	1.70 ± 0.43^{ns}
MS5	1.00 ± 0.71	1.40 ± 0.51^{ns}	1.88 ± 0.19^{*b}	1.74 ± 0.37^{*b}
MS6	0.97 ± 0.61	1.45 ± 0.15^{ns}	1.79 ± 0.11^{*b}	2.01 ± 0.52^{ns}
MS7	0.90 ± 0.84	1.10 ± 0.08^{ns}	1.33 ± 0.12^{*b}	1.30 ± 0.06^{*b}
MS8	0.91 ± 0.76	1.11 ± 0.10^{ns}	1.43 ± 0.16^{*b}	1.28 ± 0.19^{*b}
MS9	0.91 ± 0.72	1.13 ± 0.77^{ns}	1.42 ± 0.13^{*b}	1.29 ± 0.37^{*b}
MS10	0.90 ± 0.08	1.20 ± 0.31^{ns}	1.36 ± 0.09^{*b}	1.30 ± 0.58^{ns}
MS11	0.91 ± 0.12	1.59 ± 0.28^{ns}	2.09 ± 0.80^{ns}	2.00 ± 0.32^{ns}

Values are expressed as mean ± SEM. *a - significantly different from normal control and *b significantly different from toxic control at P<0.01. ns – Non-significant.

It was reported that the synthetic compounds with chloro and methoxy groups at the para position have been favorable for analgesic and anti-inflammatory activity [26, 27]. Chalcone with methoxy substitution at para position on ring B showed potent anti-inflammatory activity, as reported earlier [19]. All synthetic compounds except MS1 & MS11 showed significant anti-inflammatory activity in rats compared to the toxic control group. Among the 11 compounds synthesized, four compounds (MS7 to MS10), which contain electron-withdrawing substituents *viz*., chloro,

fluoro, bromo, and trifluoromethyl respectively in Ring B, were found to be equally potent as indomethacin throughout the study. Methoxy substituted compound, MS2, also possesses a good activity at 1 h after carrageenan treatment. However, the compounds containing electron-donating groups (MS3 to MS6) also showed moderate activity, and MS11, which contains hydroxyl group and unsubstituted MS1, was found not to possess any activity throughout the study. The effect of all the synthesized compounds and standard at 1 h after carrageenan treatment is given in **Fig. 1.**

TABLE 3: PERCENTAGE INHIBITION OF RAT PAW VOLUME OF VARIOUS SYNTHETIC COMPOUNDS ON CARRAGEENAN-INDUCED EDEMA

Treatment	% inhibition of edema after carrageenan injection		
	30min	1h	2h
Normal	---------	---------	---------
Toxic	---------	---------	---------
Standard	42.33	61.98	59.93
MS1	14.29	29.23	21.52
MS2	39.15	57.60	45.03
MS3	17.46	40.05	33.11
MS4	26.45	42.69	43.71
MS5	25.93	45.02	42.38
MS6	23.28	47.66	33.44
MS7	41.79	61.11	56.95
MS8	41.26	58.18	57.61
MS9	40.21	58.47	57.28
MS10	36.51	60.23	56.95
MS11	15.87	38.88	33.77

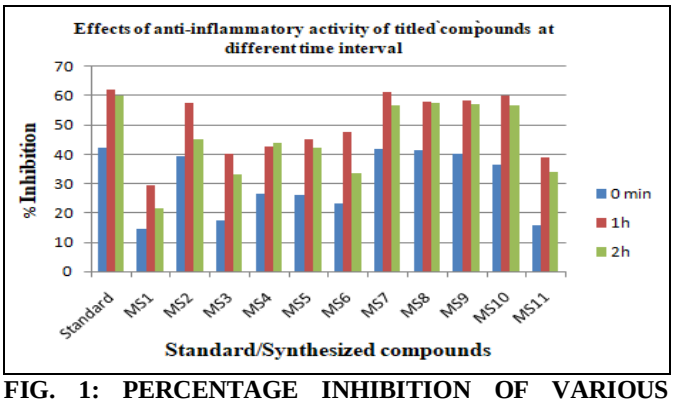


FIG. 1: PERCENTAGE INHIBITION OF VARIOUS SYNTHETIC COMPOUNDS IN DIFFERENT TIME ON CARRAGEENAN-INDUCED RAT PAW EDEMA MODEL.

Leukocytes play an important role in inflammatory conditions and they can produce cellular damage in host tissues during the same. Inhibition of leukocytes migration is a prime aim of anti-inflammatory drugs in therapeutic intervention. The effect of various synthetic drugs and standard on carrageenan-induced pleurisy and leukocytes migration in rats was shown in **Table 4.** The tests performed in the pleurisy model showed that the few of the synthetic compounds behave as inhibitors of leukocyte migration and the formation of pleural exudates when given orally, as reported earlier [28]. Results revealed that the compounds MS2, MS6 to MS10 were found to possess a significant reduction in pleural exudates and leukocytes migration when compared against toxic control. The compounds MS1, MS3, MS4, MS5, and MS11 did not seem to possess significant activity.

TABLE 4: RESULTS OF ANTI-INFLAMMATORY EFFECT OF METHANESULFONYL SUBSTITUTED CHALCONES AGAINST CARRAGEENAN INDUCED PLEURISY IN RATS

Treatment	Pleural exudates (ml)	Leukocytes ($\times 10^3$ cells/ml)
Normal control	0.10 ± 0.02	0.34 ± 0.02
Toxic control	0.36 ± 0.09*a	4.15 ± 0.35*a
Indomethacin	0.14 ± 0.03*b	0.46 ± 0.04*b
MS1	0.27 ± 0.06*b	4.04 ± 0.10^{ns}
MS2	0.17 ± 0.05*b	0.98 ± 0.07*b
MS3	0.29 ± 0.04*b	4.02 ± 0.15^{ns}
MS4	0.20 ± 0.05*b	3.53 ± 0.05^{ns}
MS5	0.20 ± 0.09*b	3.99 ± 0.96^{ns}
MS6	0.19 ± 0.07*b	2.12 ± 0.04*b
MS7	0.15 ± 0.09*b	0.51 ± 0.06*b
MS8	0.18 ± 0.06*b	0.57 ± 0.09*b
MS9	0.17 ± 0.05*b	0.55 ± 0.06*b
MS10	0.16 ± 0.04*b	0.56 ± 0.07*b
MS11	0.20 ± 0.08*b	3.52 ± 0.04^{ns}

Values are expressed as mean ± SEM. *a - significantly different from normal control and *b significantly different from toxic control at P<0.01. ns – Non significant.

TABLE 5: EFFECTS OF VARIOUS SYNTHETIC COMPOUNDS ON ACETIC ACID–INDUCED WRITHING RESPONSE IN RATS

Treatment	Number of writhing movements (Mean ± SEM)	% Inhibition
Distilled water	32.00 ± 2.52	---
Diclofenac sodium	5.95 ± 0.94*	81.40
MS1	15.30 ± 1.70*	52.18
MS2	9.30 ± 1.58*	70.93
MS3	14.62 ± 1.36*	54.31
MS4	14.82 ± 1.20*	53.68
MS5	17.51 ± 1.52*	45.28
MS6	15.55 ± 1.48*	51.40
MS7	7.90 ± 1.39*	75.31
MS8	7.81 ± 1.08*	75.59
MS9	9.91 ± 1.56*	69.03
MS10	9.65 ± 1.04*	69.84
MS11	17.96 ± 1.18*	43.75

All values are expressed as mean ± SEM (n = 6)
*Values are significantly different from group 1 at P<0.01.

Acetic Acid-Induced Writhing Response: The analgesic activity was assessed by the acetic acid-induced writhing test, which has been reported to be useful for the investigation of peripheral antinociceptive activity and performed as a chemical pain model. The analgesic activity of the titled compounds against acetic acid-induced writhing response is shown in **Table 5.**

The findings of this analgesic study revealed that the application of 10 mg/kg of various synthetic drugs had a significant analgesic effect in the animals under investigation. Among those compounds, MS7, MS8, and MS2 possess a significant analgesic effect when compared to standard. These compounds, which contain chloro, fluoro, and methoxy groups, respectively, may be responsible for the antinociceptive activities.

CONCLUSION: In this study, novel methane-sulfonyl chalcones were synthesized with different electron-withdrawing and electron donating groups. These compounds were then screened for their analgesic and anti-inflammatory potential. The study revealed that the methanesulfonyl chalcones with electron-withdrawing groups, especially halogen-substituted compounds, show a significant effect as compared to that produced by the standard drug. Further studies on the biochemical pathways may result in the development of a potent analgesic and anti-inflammatory agent with low toxicity and a better therapeutic index.

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