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Research Article

Green Chemical Synthesis and Analgesic Activity of Fluorinated Thiazolidinone, Pyrazolidinone, and Dioxanedione Derivatives

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Facile lemon juice catalyzed green and efficient synthesis of a series of new classes of 5-(fluorinatedbenzylidene)-2-thioxo-1,3-thiazolidin-4-ones **(3a–e)**, 5-methyl-4-(fluorinatedbenzylidene)-2-phenylpyrazolidin-3-ones **(5a–e)**, and 2,2-dimethyl-5-(fluorinatedbenzylidene)-1,3-dioxane-4,6-diones **(7a–e)** by the reaction of fluorinated aromatic aldehydes with active methylene compounds is reported. Lemon juice is natural acid catalyst which is readily available, cheap, nontoxic, and ecofriendly. This method is experimentally simple, clean, high yielding, green, and with reduced reaction times. The product is purified by simple filtration followed by washing with water and drying process. Some of the synthesized compounds have been evaluated "in vivo" for their analgesic activity and all the synthesized compounds are characterized by IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and mass spectral studies.

1. Introduction

The steady growth of interest in the synthesis of heterocyclic compounds is connected with their raised biological activity and also with the fact that these compounds make possible the development of novel materials of unique properties. Pyrazolone is a biologically important scaffold associated with multiple pharmacological activities such as antimicrobial [1], anti-inflammatory [2], analgesic [3], antidepressant [4], anticonvulsant [5], antidiabetic [6], antihyperlipidemic [7], antiviral [8], antitubercular [9], antioxidant [10], and anticancer activites [11, 12]. The synthesis of pyrazolone and its derivatives has engrossed substantial attention from organic and medicinal chemists for many years as they belong to a class of compounds with proven utility in medicinal chemistry.

One very interesting and promising class of heterocycles is the 4-thiazolidinone ring system. It represents a class of chemical products with interesting pharmacological and biological activities [13–18] including antidiabetic, antitubercular, anti-HIV, antiparasitic, hypnotic, and anathematic agents. Furthermore, the reactivity of the Meldrum's acid (2,2-dimethyl-1,3-dioxan-4,6-dione) as a methylene active compound was explored about 40 years after its preparation, when the structure was correctly attributed by Davidson and Bernhard [19] assigning the acidic proton to the central carbon, and its high acidity is still object of study [20]. It is known that the Meldrum's acid undergoes standard Knoevenagel condensation with aromatic and heteroaromatic aldehydes furnishing the corresponding arylidene derivatives, which are versatile substrates for different kinds of reactions [21, 22]. They are useful intermediates for cycloaddition reaction and for the synthesis of heterocyclic compounds with potential pharmacological activity [23].

Several methods have been developed for the preparation of thiazolidinone, pyrazolone, and dioxanedione derivatives. The most common is Knoevenagel condensation between aromatic aldehydes and various active methylene compounds carried out in glacial acetic acid containing anhydrous sodium acetate [24]. Instead of sodium acetate, acetic anhydride [25], ethanolamine [26], and ammonium chloride in ammonia [27–29] have also been used as catalysts. Other

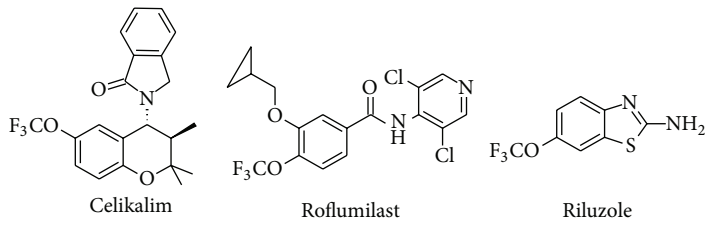


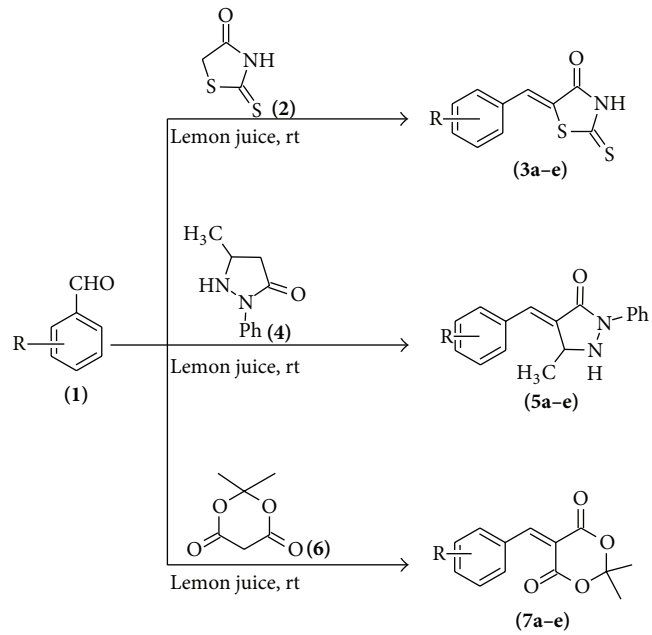
Figure 1: Fluorine containing drugs.

derivatives were also prepared using glycine and sodium carbonate as catalysts, ionic liquid, and acidic alumina as solid support, borate zirconia [30–34].

More recent methods for the preparation of 5-benzylidene-2-thioxothiazolidin-4-ones, 4-arylidene-3-methyl-1-phenyl-5-pyrazolone derivatives, and 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-dione have been reported which involve Knoevenagel condensation of aromatic aldehydes with 2-thioxothiazolidin-4-one/3-methyl-1-phenyl-1H-pyrazol-5(4*H*)-one/Meldrum acid catalyzed by a basic functionalized ionic liquid [35], nanoparticles [36, 37], triphenylphosphine [38], and 1-butyl-3-methylimidazolium hydroxide ([bmim][OH]) [39, 40]. Knoevenagel condensation is also reported under microwave irradiation for the synthesis of 5-arylidene-4-thiazolidinones [41]. These derivatives are also synthesized using tetrabutylammonium bromide (TBAB) as a phase transfer catalyst in water under microwave irradiation [42]. However, in spite of their utility, some methods suffer from disadvantages like long reaction times, low yields, chemical hazards, and environmental pollution.

In recent years, organic research is mainly focused on the development of green methods to synthesize various organic compounds through the use of alternative green catalyst to replace hazardous strong acidic or basic catalyst commonly used in organic synthesis. Nowadays, many organic transformations have been carried out using biocatalysts or intact plant systems. Recently, use of lemon juice as natural catalyst is reported [43] in few chemical reactions because it is inexpensive, most abundant in nature, nonhazardous, and ecofriendly. It exhibits unique reactivity and selectivity. As lemon juice is acidic in nature (pH ≈ 2-3) and percentage of citric acid (5%–7%) is more than other acids, it works as acid catalyst.

In addition, incorporation of fluorine further enhances the biological activity by increasing solubility in lipoid material and fat deposits in the body. Compounds of medicinal interest containing trifluoromethyl substituents, including anaesthetics, antipsychotics, antibiotics and a few antimalarials were reviewed in 1958 [44]. Antibiotic multi drug resistance is a major and continuing public health concern and some clinicians are switching to replacements such as the fluoroquinolones [45]. A recent review [46] has highlighted pesticides containing the CF_3O group, and its authors have argued that a CF_3O substituent can advantageously replace a fluorine atom in most molecules with the benefit of increased lipid solubility. Many drugs with enhanced effectiveness and selectivity contain the CF_3O moiety (e.g., celikalim, roflumilast and riluzole) (Figure 1).



R = 3-F; 4-OCF_3; 4-CF_3; 2-NO_2, 4-CF_3; 2-F, 5-NO_2

Scheme 1

In Scheme 1, we have synthesized for the first time a series of new class of fluorine containing olefinic compounds from Knoevenagel condensation of fluoro-substituted aromatic aldehydes **(1)** with active methylene compounds, 2-thioxo-4-thiazolidinone **(2)**/3-methyl-1-phenyl-2-pyrazolin-5-one **(4)**/Meldrum's acid **(6)** in the presence of lemon juice as natural acid catalyst at room temperature. The compounds synthesized by various methods have been characterized by their melting points, elemental analyses, IR, ^{1}HNMR, ^{13}CNMR, ^{19}FNMR, and mass spectral studies.

2. Results and Discussion

In continuation to our interest on environmentally benign synthesis of heterocyclic compounds [47–50], we now report the green synthesis of fluorinated thiazolidinone **(3a–e)**, pyrazolidinone **(5a–e)** and dioxanedione derivatives **(7a–e)** via Knoevenagel condensation at room temperature in the presence of catalytic amount of lemon juice as natural acid catalyst (Scheme 1). We have extensively studied the title reaction taking two parameters, namely, type of catalysts and type of solvent. In order to optimize the reaction conditions,

Table 1: Synthesis of 5-benzylidene-2-thioxo-1,3-thiazolidin-4-one **3a** under different catalysts.

Entry	Catalyst	Solvent/temperature (°C)	Time (hrs)	Yield (%)
1	Boric acid	H_2O/80	5	67
2	Oxalic acid	H_2O/80	5	72
3	Alum	H_2O/80	3	82
4	Lemon juice	H_2O/80	3	84

Table 2: Synthesis of 5-benzylidene-2-thioxo-1,3-thiazolidin-4-one **(3a)** under different solvents.

Entry	Catalyst	Solvent/temperature (°C)	Time (hrs)	Yield (%)
1	Lemon juice	EtOH/78	4	75
2	Lemon juice	CH_3OH/65	4	72
3	Lemon juice	CH_2Cl_2/40	5	66
4	Lemon juice	Room temperature	1.5	92

the synthesis of compound **3a** was used as a model reaction and a mixture of 3-fluoro benzaldehyde and 2-thioxo-4-thiazolidinone was magnetically stirred in presence of various catalysts as shown in Table 1. When reaction was carried out in aqueous medium in the presence of oxalic acid, boric acid, alum, and lemon juice (Table 1, entry 1–4), lemon juice provided the best yield as compared to other catalysts.

Furthermore, we studied the role of solvent on the synthesis of title compounds and found that the solvent played a crucial role in this reaction (Table 2, entry 1, 2, 3). Ethanol, methanol, dichloromethane were all able to facilitate but it took longer time (4-5 hrs) to complete the reaction with low yield (66–75%) of the product. We extended our studies and carried out the reaction in the absence of any solvent and presence of lemon juice at room temperature, 92% yield of the product was obtained in 1.5 hrs. (Table 2, entry 4). With these optimal conditions in hand, we examined the scope of this Knoevenagel condensation reaction. Results indicate that lemon juice is the best catalyst at room temperature for the synthesis of olefinic compounds (Table 3). As lemon juice is acidic in nature (pH ≈ 2-3) and percentage of citric acid (5%–7%) is more than other acids, it works as acid catalyst for the synthesis of fluorinated thiazolidinone **(3a–e)**, pyrazolidinone **(5a–e)**, and dioxanedione derivatives **(7a–e)**. Using this methodology, these reactions were completed in shorter reaction times (1-2 hrs) at room temperature (25°C) with yields of the product ranging from 90% to 95%. For the Knoevenagel condensation reaction, we have used extract of *Citrus limonum* species of lemon as natural catalyst for synthesis of arylidenes. To our satisfaction, we found that the use of 2 mL of lemon juice resulted in quantitative yield (90%–95%) of the corresponding olefinic compounds within 1 to 2 hrs. The purity of the compounds was checked by TLC using silica gel-G as adsorbent. We have also carried out this reaction using citric acid separately; reaction took place successfully as observed on TLC.

The product is isolated in pure form and does not require further purification and crystallization. Hence, other compounds were also synthesized at room temperature following the similar procedure. The chemical structures all the synthesized compounds have been confirmed by IR, ^{1}HNMR, ^{19}FNMR, ^{13}CNMR, and mass spectral studies.

The IR spectra of **3a–e** showed absorption bands at 3320–3350 cm^{-1} due to NH stretching of amide, 1680–1692 cm^{-1} due to C=O, 1578–1596 cm^{-1} due to C=C, and 1131–1211 cm^{-1} due to C=S Stretching, which confirms with the formation of compounds **3a–e**. The ^{1}HNMR spectrum of **3b** showed peaks at δ 8.65 (s, 1H, NH), 8.02 (s, 1H, CH), and 6.79–7.98 (m, 4H, Ar-H) ppm. Formation of compound **3b** was further confirmed on the basis of ^{13}CNMR spectrum. In the ^{13}CNMR spectrum, sharp signals were observed at δ 200 (C=S), 168.37 (C=O), 161.23 (C-O), 143 (CH), 120.48 (C=C, aliphatic carbon), 122 (OCF_3), and 138.25–119.36 (aromatic carbons) ppm. Mass spectrum of compound **3b** showed molecular ion peak [$M^+ + 1$] at 306 m/z (54%) corresponding to its molecular weight along with base peak observed at m/z 122 (100%) and other relevant peaks were observed at m/z 246 (39%), 236 (84%), 220 (70%), 95 (15%), and 79 (58%).

The IR spectra of **5a–e** showed absorption bands at 2915–3129 cm^{-1} due to CH str of methine, 1670–1688 cm^{-1} due to C=O str, and 1586–1591 cm^{-1} due to C=C, which confirms with the formation of compounds **5a–e**. The ^{1}HNMR spectrum of **5d** showed peaks at δ 7.73 (s, 1H, CH), 7.19–7.71 (comp, 8H, Ar-H), 3.51 (s, 1H, CH), 2.52 (s, 1H, NH), and 1.24 (s, 3H, CH_3) ppm. Formation of compound **5d** was further confirmed on the basis of ^{13}CNMR spectrum. In the ^{13}CNMR spectrum, sharp signals were observed at δ 162.50 (C=O), 134.82 (CH), 130.82 (C=C, aliphatic carbon), 123.13 (CF_3), 139.82–112.12 (aromatic carbons), and 21.73 (CH_3) ppm.

The IR spectra of **7a–e** showed absorption bands at 2915–3083 cm^{-1} due to CH str of methine, 1630–1685 cm^{-1} due to C=O str, 1554–1590 cm^{-1} due to C=C, and 1055–1145 cm^{-1} (C-O) which confirms with the formation of compounds. The ^{1}HNMR spectrum of **7a** showed peaks at δ 8.97 (s, 1H, CH), 7.70–7.84 (m, 4H, Ar-H), and 2.12 (s, 6H, CH_3) ppm. Formation of compound **7a** was further confirmed on the basis of ^{13}CNMR spectrum. In the ^{13}CNMR spectrum, sharp signals were observed at δ 164.91 (C=O), 160.42 (C-F), 154.08 (CH), 123.74 (C=C, aliphatic carbon), 134.02–118.12 (aromatic carbons), 105.18 (O-C-O), and 26.16 (CH_3) ppm. The mass spectrum of compound **7a** showed molecular ion peak [M^+] at 250 m/z (30%) corresponding to its molecular weight along with base peak observed at m/z 176 (100%) and other relevant peaks were observed at m/z 123 (13%), 100 (34%), and 63 (9%). Spectral analyses of all the synthesized compounds are given in Tables 4, 5, and 6.

3. Experimental

General. Reagents and solvents were obtained from commercial sources and used without further purification. Melting points were determined on a Toshniwal apparatus. The ^{1}H NMR and ^{13}C NMR of synthesized compounds have been carried out at SAIF, Punjab University, Chandigarh, India.

Table 3: Experimental and analytical data of 5-(fluorinatedbenzylidene)-2-thioxo-1,3-thiazolidin-4-ones **(3a–e)**, 5-methyl-4-(fluorinated-benzylidene)-2-phenylpyrazolidin-3-ones **(5a–e)**, and 2,2-dimethyl-5-(fluorinatedbenzylidene)-1,3-dioxane-4,6-diones **(7a–e)**.

Entry	R	Time (hrs/min)	Yield (%)	M.P. (°C)	Analysis calcd. (found) (%)		
					C	H	N
3a	3-F	1.5 hrs	95	132	50.19 (50.04)	2.53 (2.50)	5.85 (5.88)
3b	4-OCF_3	1 hrs	90	115	43.28 (43.08)	1.98 (1.95)	4.59 (4.61)
3c	4-CF_3	70 min	92	172	45.67 (45.35)	2.09 (2.07)	4.84 (4.82)
3d	2-NO_2, 4-CF_3	100 min	91	110	39.52 (39.75)	1.51 (1.53)	8.38 (8.35)
3e	2-F, 5-NO_2	2 hrs	94	89	42.25 (42.05)	1.77 (1.75)	9.85 (9.81)
5a	3-F	40 min	90	102	72.32 (72.15)	5.36 (5.33)	9.92 (9.95)
5b	4-OCF_3	50 min	93	85	62.07 (62.25)	4.34 (4.36)	8.04 (8.00)
5c	4-CF_3	1 hrs	94	105	65.06 (65.25)	4.55 (4.52)	8.43 (8.40)
5d	2-NO_2, 4-CF_3	60 min	90	162	57.30 (57.08)	3.74 (3.72)	11.14 (11.11)
5e	2-F, 5-NO_2	70 min	93	180	62.38 (62.20)	4.31 (4.34)	12.84 (12.82)
7a	3-F	1.5 hrs	91	104	62.40 (62.56)	4.43 (4.45)	—
7b	4-OCF_3	2 hrs	90	143	53.17 (53.34)	3.51 (3.49)	—
7c	4-CF_3	2 hrs	95	164	56.01 (56.22)	3.69 (3.67)	—
7d	2-NO_2, 4-CF_3	2 hrs	92	110	48.71 (48.51)	2.92 (2.94)	4.06 (4.03)
7e	2-F, 5-NO_2	160 min	94	115	52.89 (52.69)	3.41 (3.39)	4.74 (4.71)

Table 4: Spectral data of 5-(fluorinatedbenzylidene)-2-thioxo-1,3-thiazolidin-4-ones **(3a–e)**.

Entry	IR (cm^{-1})	^{1}H NMR (δ ppm)	^{13}C NMR (δ ppm)
3a	3350 (NH str of amide), 1590 (C=C), 1131 (C=S str), 1680 (C=O)	8.01 (s, 1H, NH), 7.42 (s, 1H, CH), 7.14 (d, 2H, Ar-H, J = 8.2 Hz), 7.30 (d, 2H, Ar-H, J = 8.2 Hz)	200 (C=S), 168.31 (C=O), 142.33 (CH), 120.48 (C=C, aliphatic carbon), 138.25–119.36 (aromatic carbons)
3b	3357 (NH str of amide), 1596 (C=C), 1211 (C=S str), 1682 (C=O)	8.65 (s, 1H, NH), 8.02 (s, 1H, CH), 7.98 (d, 2H, Ar-H, J = 8.0 Hz), 6.79 (d, 2H, Ar-H, J = 8.0 Hz)	200 (C=S), 168.37 (C=O), 161.23 (C–O) 143 (CH), 120.48 (C=C, aliphatic carbon), 122 (CF_3), 138.25–119.36 (aromatic carbons)
3c	3348 (NH str of amide), 1578 (C=C), 1168 (C=S str), 1686 (C=O)	8.32 (s, 1H, NH), 7.50 (s, 1H, CH), 7.46 (d, 2H, Ar-H, J = 8.5 Hz), 7.32 (d, 2H, Ar-H, J = 8.5 Hz)	198.55 (C=S), 169.30 (C=O), 143 (CH), 120.48 (C=C, aliphatic carbon), 122.06 (CF_3), 138.25–119.92 (aromatic carbons)
3d	3320 (NH str of amide), 1590 (C=C), 1136 (C=S str), 1688 (C=O)	8.62 (s, 1H, NH), 7.50 (s, 1H, CH), 7.43 (s, 1H, Ar-H), 7.26 (d, 2H, Ar-H, J = 8.2 Hz)	201 (C=S), 168.32 (C=O), 143.44 (CH), 121.17 (C=C, aliphatic carbon), 118.56 (CF_3), 146.25–120.36 (aromatic carbons)
3e	3342 (NH str of amide), 1584 (C=C), 1161 (C=S str), 1692 (C=O)	8.51 (s, 1H, NH), 7.44 (s, 1H, Ar-H), 7.28 (d, 2H, Ar-H, J = 8.0 Hz)	200 (C=S), 168.37 (C=O), 161.03 (C–F), 143 (CH), 120.48 (C=C, aliphatic carbon), 138.25–119.36 (aromatic carbons)

Table 5: Spectral data of 5-methyl-4-(fluorinatedbenzylidene)-2-phenylpyrazolidin-3-ones **(5a–e)**.

Entry	IR (cm^{-1})	^{1}H NMR (δ)	^{13}C NMR (δ)
5a	3129 (CH), 1670 (C=O), 1586 (C=C)	7.42 (s, 1H, CH), 7.14–7.30 (comp, 9H, Ar-H), 3.48 (s, 1H, CH), 2.01 (s, 1H, NH), 1.20 (s, 3H, CH_3)	163.17 (C–F), 161.31 (C=O), 135.33 (CH), 130.48 (C=C, aliphatic carbon), 142.05–115.16 (aromatic carbons), 24.13 (CH_3)
5b	3073 (CH), 1677 (C=O), 1586 (C=C)	7.67 (s, 1H, CH), 7.38–7.20 (comp, 9H, Ar-H), 3.46 (s, 1H, CH), 2.11 (s, 1H, NH), 1.23 (s, 3H, CH_3)	162.17 (C–O), 161.40 (C=O), 133.68 (CH), 130.83 (C=C, aliphatic carbon), 122 (CF_3), 141.85–114.32 (aromatic carbons), 23.93 (CH_3)
5c	2915 (CH), 1675 (C=O), 1589 (C=C)	7.50 (s, 1H, CH), 7.34–7.17 (comp, 9H, Ar-H), 3.48 (s, 1H, CH), 2.08 (s, 1H, NH), 1.53 (s, 3H, CH_3)	161.78 (C=O), 135.21 (CH), 130.83 (C=C, aliphatic carbon), 122.54 (CF_3), 141.08–115.36 (aromatic carbons), 23.40 (CH_3)
5d	3060 (CH), 1688 (C=O), 1591 (C=C)	7.73 (s, 1H, CH), 7.19–7.71 (comp, 8H, Ar-H), 3.51 (s, 1H, CH), 2.52 (s, 1H, NH), 1.24 (s, 3H, CH_3)	162.50 (C=O), 134.82 (CH), 130.82 (C=C, aliphatic carbon), 123.13 (CF_3), 139.82–112.12 (aromatic carbons), 21.73 (CH_3)
5e	3069 (CH), 1678 (C=O), 1590 (C=C)	7.62 (s, 1H, CH), 7.38–7.27 (comp, 8H, Ar-H), 3.40 (s, 1H, CH), 2.14 (s, 1H, NH), 1.25 (s, 3H, CH_3)	161.97 (C–F), 161.54 (C=O), 135.33 (CH), 136.40 (C=C, aliphatic carbon), 141.15–114.16 (aromatic carbons), 23.10 (CH_3)

Table 6: Spectral data of 2,2-dimethyl-5-(fluorinatedbenzylidene)-1,3-dioxane-4,6-diones (**7a–e**).

Entry	IR (cm^{-1})	^{1}H NMR (δ ppm)	^{13}C NMR (δ ppm)
7a	3083 (CH), 1630 (C=O), 1554 (C=C str), 1055 (C–O)	8.97 (s, 1H, CH), 7.70 (d, 2H, Ar-H, J = 8.1 Hz), 7.64 (d, 2H, Ar-H, J = 8.1 Hz), 2.12 (s, 6H, CH_3)	164.91 (C=O), 160.42 (C–F), 154.08 (CH), 123.74 (C=C, aliphatic carbon), 134.02–118.12 (aromatic carbons), 105.18 (O–C–O), 26.16 (CH_3)
7b	2915 (CH), 1682 (C=O), 1577 (C=C str), 1130 (C–O)	8.42 (s, 1H, CH), 7.61 (d, 2H, Ar-H, J = 8.2 Hz), 7.32 (d, 2H, Ar-H, J = 8.0 Hz), 1.83 (s, 6H, CH_3)	164.27 (C–O), 165.46–165.30 (C=O), 150.03 (CH), 124.18 (C=C, aliphatic carbon), 122.42 (CF_3), 134.85–120.06 (aromatic carbons), 107.92 (O–C–O), 27.12–26.97 (CH_3)
7c	3072 (CH), 1680 (C=O), 1583 (C=C str), 1145 (C–O)	8.77 (s, 1H, CH), 7.88 (d, 2H, Ar-H, J = 7.9 Hz), 7.47 (d, 2H, Ar-H, J = 7.9 Hz), 1.85 (s, 6H, CH_3)	167.40–167.30 (C=O), 149.26 (CH), 126.15 (C=C, aliphatic carbon), 122.42 (CF_3), 135.05–121.93 (aromatic carbons), 106.94 (O–C–O), 27.72–27.64 (CH_3)
7d	3060 (CH), 1685 (C=O), 1584 (C=C str), 1095 (C–O)	8.81 (s, 1H, CH), 7.80 (s, 1H, Ar-H), 7.43 (d, 2H, Ar-H, J = 6.5 Hz), 1.75 (s, 6H, CH_3)	166.22–166.10 (C=O), 149.29 (CH), 126.85 (C=C, aliphatic carbon), 123.67 (CF_3), 135.95–122.33 (aromatic carbons), 107.04 (O–C–O), 27.72–27.60 (CH_3)
7e	2979 (CH), 1680 (C=O), 1590 (C=C str), 1130 (C–O)	8.37 (s, 1H, CH), 7.55 (s, 1H, Ar-H), 7.17 (d, 2H, Ar-H, J = 7.3 Hz), 1.70 (s, 6H, CH_3)	165.40–165.30 (C=O), 163.22 (C–F), 146.91 (CH), 127.05 (C=C, aliphatic carbon), 134.35–120.63 (aromatic carbons), 106.97 (O–C–O), 26.50–26.42 (CH_3)

IR spectra of compounds have been carried out at FET, MITS, Laxmangarh, Sikar, Rajasthan, India. The purity of compounds was checked on thin layers of silica gel in various nonaqueous solvent systems, for example, ethyl acetate : *n*-hexane (1 : 9). IR spectra were recorded in KBr on a PerkinElmer Infrared L1600300 Spectrum Two Li Ta spectrophotometer and ^{1}H NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer using DMSO-d_6 and $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference standard. The analgesic activity of synthesized compounds was carried out in Goenka College of Pharmacy, Department of Pharmacology, Lakshmangarh, Sikar, Rajasthan, India.

General Procedure for Extraction of Lemon Juice. Fresh lemon was cut by using knife and then pieces were pressed manually using domestic presser to extract juice. Then juice was then filtered through cotton/muslin cloth and then through filter paper to remove solid material and to get clear juice which was used as a catalyst.

*General Procedure for the Preparation of **3a–e**, **5a–e**, and **7a–e***. A mixture of fluorinated aromatic aldehyde (1 mmol) and 2-thioxo-4-thiazolidinone/3-methyl-1-phenyl-2-pyrazolin-5-one/Meldrum's acid (1 mmol) was taken in single neck round bottom flask and to this lemon juice (2 mL) was added as catalyst. The reaction mixture was stirred at room temperature for the appropriate time required for the completion of reaction given in Table 2. The progress of reaction was monitored by TLC using ethyl acetate : *n*-hexane (1 : 9) as eluent. After the completion of the reaction, mixture was poured onto crushed ice, and the solid product obtained was filtered and isolated in pure form with no need of further purification. For comparative studies, **3a** was synthesized using various solvents and catalysts. Results of synthesis of **3a** under different reaction conditions are given in Tables 1 and 2. The structures of the newly synthesized compounds are determined on the basis of their FTIR, ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, and mass spectral data.

4. Analgesic Activity

Few compounds have been screened for analgesic activity. The analgesic properties of the target compounds were tested using a model of central analgesia where the painful stimulus is represented by a hot plate heated to 56°C. Seven groups of 6 mice, each having an average weight of 25–35 g, were taken for study. The animals were kept for a week before the experiment under standard laboratory environment, with access to water *ad libitum*. The experiment consisted in measuring the reaction to pain as the time (in seconds) between the moment when the animal was placed on the plate and the moment when it begins to lick its back paws in response to painful stimulus.

The animals were treated as follows.

Group 1: control group received 0.5% sodium CMC (1 mg/kg) I.P.

Group 2: nimesulide 5 mg/kg was administered I.P.

Group 3: the **3a** in dose level of 50 mg/kg was administered I.P.

Group 4: the **3b** in dose level of 50 mg/kg was administered I.P.

Group 5: the **3d** in dose level of 50 mg/kg was administered I.P.

Group 6: the **5b** in dose level of 50 mg/kg was administered I.P.

Group 7: the **5d** in dose level of 50 mg/kg was administered I.P.

The time response of the animal to painful stimulus was evaluated at 0, 30, 60, and 90 minutes interval after the administration of the tested substances. The recorded results were used to calculate for each group of animals the average response time to painful stimulus and the standard error. Statistical analysis (ANOVA followed by using Dunnett's test) was performed for analgesic activity to ascertain the significance of the exhibited activity. Compounds **3b**, **5d**, and **5d**

Table 7: Analgesic activity of the fluorinated 5-Substitutedbenzylidene derivatives.

	0 min	30 min	60 min	90 min
Control	1.33 ± 0.210	1.66 ± 0.210	1.50 ± 0.223	1.83 ± 0.307
Standard Drug	1.5 ± 0.223	3.5 ± 0.428** **53%**	7.83 ± 0.477** **81%**	13.16 ± 0.166** **86%**
3a	1.16 ± 0.166	2 ± 0.258ns **17%**	2 ± 0.258ns **25%**	2.56 ± 0.210ns **27%**
3b	1.66 ± 0.210	3.16 ± 0.307** **48%**	4.83 ± 0.307** **69%**	9.66 ± 0.557** **81%**
3d	1.66 ± 0.166	1.83 ± 0.307ns **9%**	2 ± 0.258ns **25%**	2.56 ± 0.210ns **27%**
5b	1.5 ± 0.223	3.16 ± 0.307** **48%**	5.5 ± 0.223** **73%**	10.83 ± 0.600** **83%**
5d	1.66 ± 0.210	3.0 ± 0.0.258** **45%**	4.5 ± 0.428** **67%**	8.52 ± 0.670** **78%**

All values mean ± S.E.M values using 6 animals in each group.
Significant differences with respect to control group were evaluated by ANOVA, Dunnett's test.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ns: nonsignificant.

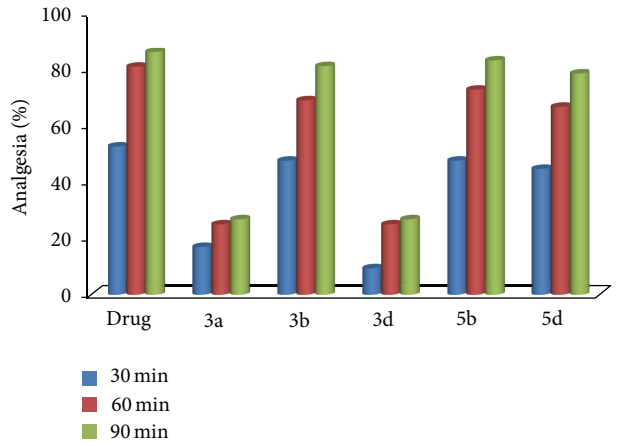


Figure 2: Comparison of the analgesic activity exhibited (%) by the test and standard compounds at time interval of 30 min, 60 min and 90 min.

have shown excellent analgesic activity as compared to other compounds which indicate that OCF_3 group is more potent than CF_3 and NO_2 groups (Table 7, Figure 2).

5. Conclusion

The use lemon juice as green catalyst offers a convenient, nontoxic, inexpensive reaction medium for the synthesis of olefinic compounds. This procedure is simpler, economical, milder, and faster, including cleaner reactions, high yields of products and a simple experimental and work-up procedure, which makes it a useful and attractive process and is also consistent with the green chemistry theme which affords excellent yields. Compounds bearing OCF_3 group possess excellent analgesic activity. With further molecular modification and manipulation of these compounds, several other promising bioactive molecules can be developed in future.

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