Received: 19 August 2020 | Revised: 29 October 2020 | Accepted: 10 November 2020

DOI: 10.1002/jccs.202000357

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

ARTICLE

Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives via Knoevenagel condensation and their biological evaluation

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Abstract

In search of new active molecules, a small focused library of the synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) has been efficiently prepared via the Knoevenagel condensation approach. All the derivatives were synthesized by conventional and non-conventional methods like ultrasonication and microwave irradiation, respectively. Several derivatives exhibited excellent anti-inflammatory activity compared to the standard drug. Furthermore, the synthesized compounds were found to have potential antioxidant activity. In addition, to rationalize the observed biological activity data, an in silico absorption, distribution, metabolism, and excretion (ADME) prediction study also been carried out. The results of the in vitro and in silico studies suggest that the 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) may possess the ideal structural requirements for the further development of novel therapeutic agents.

KEYWORDS

ADME prediction, anti-inflammatory, antioxidant, Knoevenagel, microwave, pyrazole, ultrasonication

1 | INTRODUCTION

The pyrazole ring is a prominent heterocyclic structural compound found in several pharmaceutically active compounds. This is because of its use in pharmacological activity and ease of synthesis. Furthermore, the selective functionalization of pyrazole with diverse substituents was also found to improve their range of action in various fields. Pyrazole containing heterocycles shows various biological activity, such as antibacterial,[1] antifungal,[2] antimicrobial,[3] anti-inflammatory,[4a] antioxidant,[4b] insecticidal,[5] antiviral,[6] anti-nitric oxide synthase,[7] glycogen receptor antagonist,[8] anticancer,[9] antienzyme,[10] immunosuppressant,[11] anti-fatty acid amide hydrolase (FAAH),[12] and liver-x-receptor [LXR] partial agonist activities.[13]

Fluorine or fluorine-based compounds are of great interest in synthetic and medicinal chemistry. The position of the fluorine atom in an organic molecule plays a vital role in agrochemicals, pharmaceuticals, and materials[14] as it changes the pharmacokinetic and pharmacodynamic properties of the molecule owing to its high membrane permeability, metabolic stability, lipophilicity, and binding affinity.[15]

Perfluoro-alkylated and trifluoro-methylated pyrazoles represent pharmacologically related core structures that are present in many important drugs and agrochemicals, such as fluazolate (herbicide), penthiopyrad (fungicide), razaxaban (anticoagulant), deracoxib, celecoxib (anti-inflammatory), and penflufen (fungicidal) (Figure 1).[16] So, the modern trend is moving more in the direction of the synthesis of a collection of fluorine-containing molecules in order to find excellent biological activity.

Ultrasonic irradiation is a new technology that has been widely used in chemical reactions. When ultrasonic waves pass through a liquid medium, a large number of microbubbles form, grow, and collapse in very short times, about a few microseconds. The formation and violent collapse of small vacuum bubbles takes place due to the ultrasonication waves generated in alternating high pressure and low pressure in liquids, and the phenomenon is known as cavitation. It causes high-speed imposing liquid jets and strong hydrodynamic shear forces. The deagglomeration of nanometer-sized materials was carried out using these effects. In this aspect, for high-speed mixers and agitator bead mills, ultrasonication is an alternative.[17]

In the preparative chemist's toolkit, microwave heating is a valuable technique. Due to a modern scientific microwave apparatus, it is possible to access elevated temperatures in an easy, safe, and reproducible way.[18] In recent years, microwave-assisted organic synthesis (MAOs)[19] has been emerged as a new "lead" in organic synthesis. Important advantages of this technology include a highly accelerated rate of the reaction and a decrease in reaction time, with an increase in the yield and quality of the product. The current technique is considered an important method toward green chemistry as this technique is more environmentally friendly. The conventional method of organic synthesis usually needs a longer heating time; tedious apparatus setup, which results in the higher cost of the process; and the excessive use of solvents/reagents, which leads to environmental pollution. This growth of green chemistry

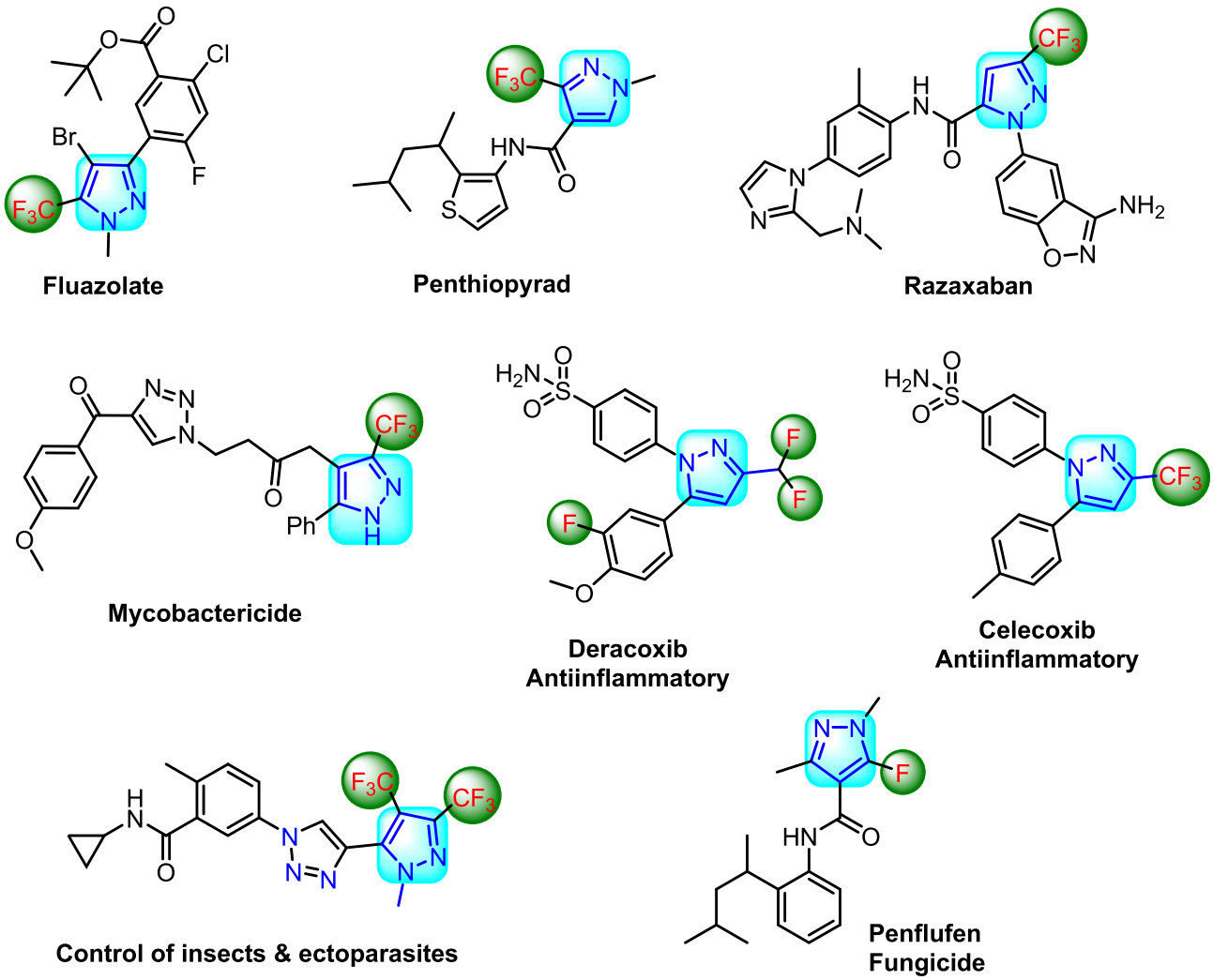


FIGURE 1 Structure of pyrazole- and fluorine-containing commercially available drugs

holds significant potential for a reduction of the byproduct, a reduction in waste production, and lowering of the energy costs. Due to its ability to couple directly with the reaction molecule and bypass thermal conductivity, leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses.[20] Knoevenagel condensation reactions are carried out by the condensation of aldehyde and the active methylene group using different catalysts such as piperidine, $InCl_3$, $TiCl_4$, LiOH, $ZnCl_2$, and $NbCl_5$.[20,21] They are also carried out using $NaAlO_2$-promoted mesoporous catalysts,[22] ionic liquid,[23] monodisperse carbon nanotube-based NiCu nanohybrids,[24] and MAOs.[25] This is one of the most important methodologies used in synthetic organic chemistry for the formation of a C—C double bond.

From our study, the results demonstrated that green methodologies are less hazardous than classical synthesis methods, as well more efficient and economical and environmentally friendly; short reaction times and excellent yields are observed for those reactions in which conventional heating is replaced by microwave irradiation. Keeping in mind the 12 principles of green chemistry, in continuation of our research work,[26] and the advantages of microwave irradiation and activities associated with pyrazole and fluorine, we construct pyrazole and fluorine in one molecular framework as new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives under conventional, as well as microwave, irradiation and ultrasonication and evaluated their anti-inflammatory and antioxidant activity. In addition to this, we have also performed in silico absorption, distribution, metabolism, and excretion (ADME) predictions for the synthesized compounds.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

A facile, economic, and green protocol for the cyclocondensation of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) with different aldehydes has been achieved.

The key starting material 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (**3**) was synthesized by the condensation of 1-(perfluorophenyl)hydrazine (**1**) and ethyl 4,4,4-trifluoro-3-oxobutanoate (**2**) in ethanol[27] (Scheme 1).

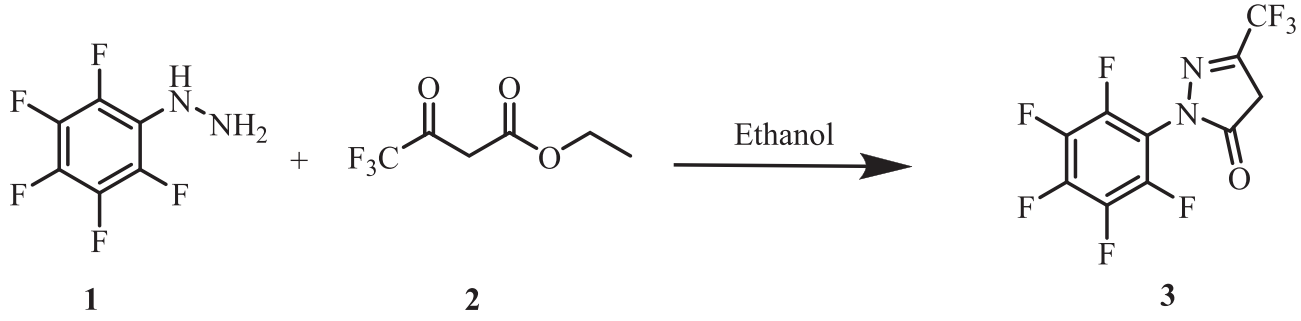
Initially, we carried out the reaction between 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (2 mmol) (**3**) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) refluxed in acetic acid as a model reaction (Scheme 2). Initially, the model reaction was carried out in ethanol without using acetic acid, and it was observed that a very low yield of product (20%) was obtained even after 2 hr. Therefore, improving the yield intervention of the catalyst was thought to be necessary. So, we decided to use acetic acid as a catalyst to promote this transformation at room temperature. At room temperature, the yield of product (45%) was found to be increased in 3 hr, so we decided to provide heating to the reaction mixture to achieve maximum product yield.

When the reaction mixture refluxed in acetic acid, product formation took place after 2 hr, and the yield of the product was 72% (Table 1).

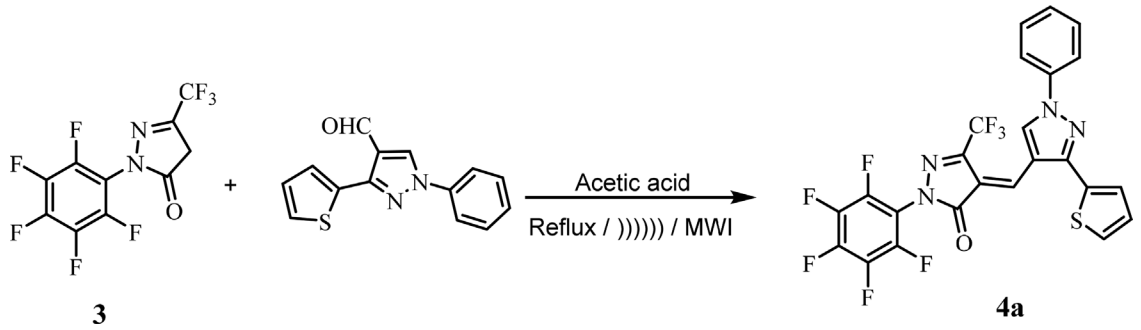
To check the ultrasonication's specific effect on this reaction, under ultrasound irradiation at 35–40°C, we carried out the model reaction using the optimized reaction conditions in hand to check whether the reaction could be accelerated with further improved product yield within a short reaction time (Scheme 2).

It was observed that, under ultrasonic conditions, the conversion rate of a reactant to product increased with less time (Table 1). Thus, when considering the basic green chemistry concept, ultrasonic irradiation was found to have a beneficial effect on the synthesis of Knoevenagel derivatives (**4a-d**, **5a-f**, and **6a-e**), which was superior to the traditional method with respect to yield and reaction time (Table 1).

To accomplish the goal and significance of green chemistry, the model reaction was carried out under



SCHEME 1 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one **3**



SCHEME 2 Model reaction for conventional, ultrasonication, and microwave irradiation methods

TABLE 1 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**)

						Conventional method[a]		Ultrasound method[b]		Microwave method[c]	
Cpd	R_1	R_2	R_3	R_4	m. p. (°C)	Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)	Time (min)	Yield[d] (%)
4a	H	H	-	-	224–226	120	72	20	81	6.5	84
4b	Br	F	-	-	232–234	120	75	18	78	6.5	81
4c	Cl	H	-	-	216–218	120	70	20	76	6.0	80
4d	Br	H	-	-	230–232	120	64	16	70	6.5	76
5a	H	H	OMe	-	202–204	120	70	21	76	5.5	84
5b	H	H	H	-	186–188	120	66	17	72	6.0	80
5c	F	H	OMe	-	180–182	120	68	16	75	7.0	82
5d	H	H	Me	-	206–208	120	65	16	71	6.5	79
5e	H	H	OCF_3	-	142–144	120	62	18	70	6.5	76
5f	H	Cl	Cl	-	212–214	120	70	19	80	5.5	84
6a	Me	Cl	Me	H	188–190	120	66	18	76	6.0	78
6b	H	Cl	Me	H	180–182	120	62	17	72	7.5	75
6c	H	Cl	H	H	176–178	120	59	18	79	7.0	80
6d	H	Cl	H	Cl	212–214	120	64	20	72	7.0	78
6e	H	H	Me	H	180–182	120	60	18	80	7.5	82

Abbreviation: Cpd, compound.

[a]Reaction conditions: Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) refluxed in acetic acid.

[b]Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) in acetic acid under ultrasound irradiation.

[c]Compound (**3**) (2 mmol) and 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (2 mmol) in acetic acid under microwave irradiation.

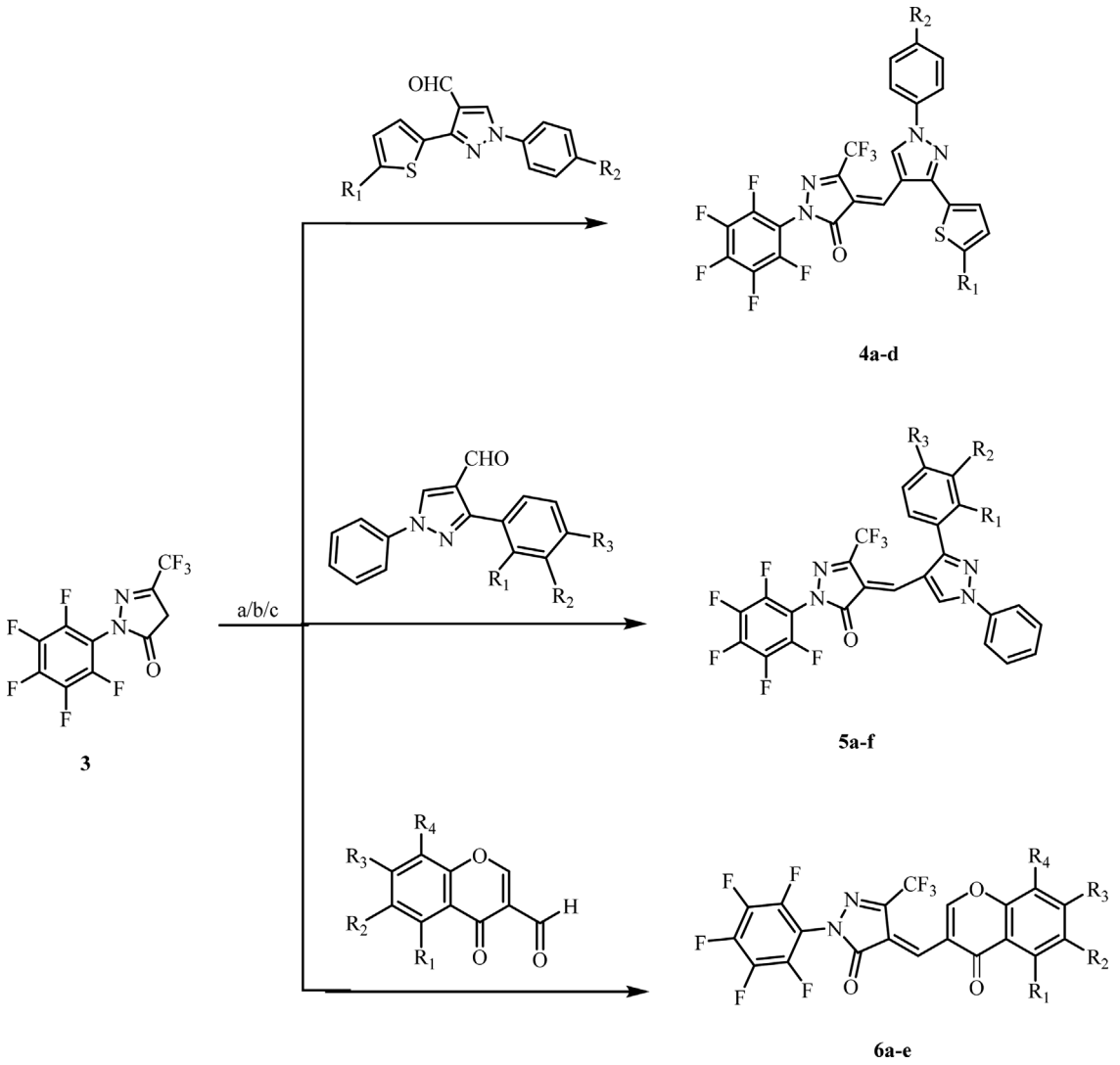
[d]Isolated yield. m.p.: melting point.

microwave irradiation for a period of time indicated in Table 1 at 350 W (Scheme 2). Fortunately, the product formation occurred in 6.5 min, with an 84% increase in yield .

So, from the above experiments, it can be concluded that, when the reaction was carried out under the conventional method, it gave comparatively low yields of products with longer reaction times, while the same reaction carried out under the influence of ultrasonic irradiation and microwave irradiation gave excellent yields of the products in short reaction times.

Finally, we assessed the scope and generality of this method for the Knoevenagel condensation between 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) and different aldehydes (Scheme 3), achieved under conventional and nonconventional methods like the ultrasound and microwave methods, respectively. With respect to the substituent present on the aromatic ring of aldehyde, under the optimized conditions, the corresponding products were obtained in high to excellent yields (Table 1).

More importantly, hetero aryl aldehydes were observed to be well tolerated under optimized conditions,



SCHEME 3 Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**). Reaction conditions: **a** = Refluxed in acetic acid. **b** = Under ultrasound irradiation in acetic acid. **c** = Under microwave irradiation using acetic acid as a solvent

furnishing the product in good yields. All the synthesized compounds (**4a-d**, **5a-f**, and **6a-e**) were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra.

The formation of (4*E*)-3-(trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one **4a-d** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. In the IR spectrum of compound **4a**, the peaks observed at 1,681 cm^{-1} indicate the presence of C═O group. In the ^{1}H NMR spectrum of compound **4a**, two singlets were observed at δ 8.11 and 10.10 ppm for pyrazolyl and olefinic proton, respectively. The ^{13}C NMR spectrum of compound **4a** revealed that the peak appearing at δ 161.4 ppm is due to the presence of carbonyl carbon. The structure of compound **4a** was also confirmed by a molecular ion peak at *m*/*z* 555.01 $(M + H)^{+}$. Similarly, the synthesis of (4*E*)-3-(trifluoromethyl)-1-(perfluorophenyl)-4-([1,3-diphenyl-1*H*-pyrazol-4-yl]methylene)-1*H*-pyrazol-5(4*H*)-ones **5a-f** was also confirmed by spectral techniques. In the IR spectrum of compound **5a**, the peak observed at 1,701 cm^{-1} corresponded to the C═O group. In the ^{1}H NMR spectrum of compound **5a**, the three singlets observed at δ 3.92, 8.11, and 10.10 ppm confirm the presence of ─OCH_3, pyrazolyl proton, and olefinic proton, respectively. The ^{13}C NMR spectrum of compound **5a** showed peaks at δ 162.5 and 55.5 ppm, confirming the presence of carbonyl carbon and methoxy carbon, respectively. Furthermore, the structure of compound **5a** was also confirmed by a molecular ion peak at *m*/*z* 573.21 $(M + H)^{+}$.

Furthermore, the formation of (*Z*)-4-([4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one **6a-e** was

confirmed by various spectral techniques. The IR spectrum of compound **6a** showed absorption peaks at 1,707 and 1,666 cm^{-1} corresponding to two carbonyl groups present in the molecules. The ^{1}H NMR spectrum of compound **6a** showed four singlets at δ 2.54 and δ 3.01 ppm for two —CH_3, δ 8.50 ppm for chromone ring proton, and δ 10.54 ppm for olefinic proton. The ^{13}C NMR spectrum of compound **6a** showed that two signals appear at δ 175.4 and 164.2 ppm for the carbonyl carbon of chromone and pyrazolone ring, respectively. In addition, two signals for methyl carbon appear at δ 22.2 and 18.6 ppm. The structure of compound **6a** was also confirmed by mass spectra and by a molecular ion peak observed at m/z 537.11 $(M + H)^+$. Similarly, all the synthesized compounds were characterized by the spectral analysis. Structures of all the synthesized derivatives are shown in Figure S1 (Supporting Information).

2.2 | Biological activity

2.2.1 | Anti-inflammatory activity

The newly synthesized 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (**4a-d**, **5a-f**, and **6a-e**) (EC_{50} range = 0.6483 ± 0.221–0.8519 ± 0.281 μg/ml) exhibited moderate anti-inflammatory activity compared to the standard drug diclofenac sodium. Among all the synthesized compounds, except compounds **4c**, **5c**, **5e**, **6d**, and **6e**, all other compounds exhibited a minimum inhibitory concentration (MIC) of 200 μg/ml compared to the standard drug diclofenac sodium (Table 2).

The percent inhibition of compounds in the in vitro anti-inflammatory model is shown in Figure 2. Furthermore, the comparative percent inhibition of compounds in the in vitro anti-inflammatory model is shown in Figure 3.

TABLE 2 Anti-inflammatory and antioxidant activity of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (MIC in μg/ml)

Compound	Anti-inflammatory	Antioxidant
4a	200	>100
4b	200	>400
4c	400	>200
4d	200	>200
5a	200	<100
5b	200	>200
5c	NT	NT
5d	200	<100
5e	800	<100
5f	200	<100
6a	200	<100
6b	200	<100
6c	200	>200
6d	800	>100
6e	400	<100
Diclofenac sodium	50	-
Ascorbic acid	-	<50

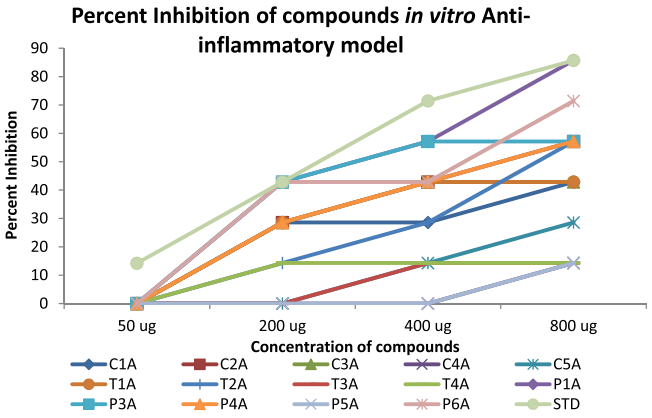


FIGURE 2 The percent inhibition of compounds in an in vitro anti-inflammatory model

2.2.2 | Antioxidant activity

In the present study, antioxidant activity of the synthesized compounds has been assessed in vitro by the DPPH radical scavenging assay.[28] Ascorbic acid (AA) has been used as a standard drug for the comparison of antioxidant activity, and the observed results are summarized in Table 2.

According to the DPPH assay, compounds **5a**, **5d**, **5e**, **5f**, **6a**, **6b**, and **6e** (IC_{50} = <100 μg/ml) exhibited excellent antioxidant activity compared to the standard antioxidant drug AA (IC_{50} = <50 μg/ml). The remaining synthesized compounds display comparable antioxidant activity than the standard drug butylated hydroxytoluene (Table 2). The percent inhibition of compounds in the in vitro antioxidant model is shown in Figure 4.

2.3 | Computational study

2.3.1 | In silico ADME

An important task for the lead compounds is early prediction of drug likeness properties as it resolves the cost

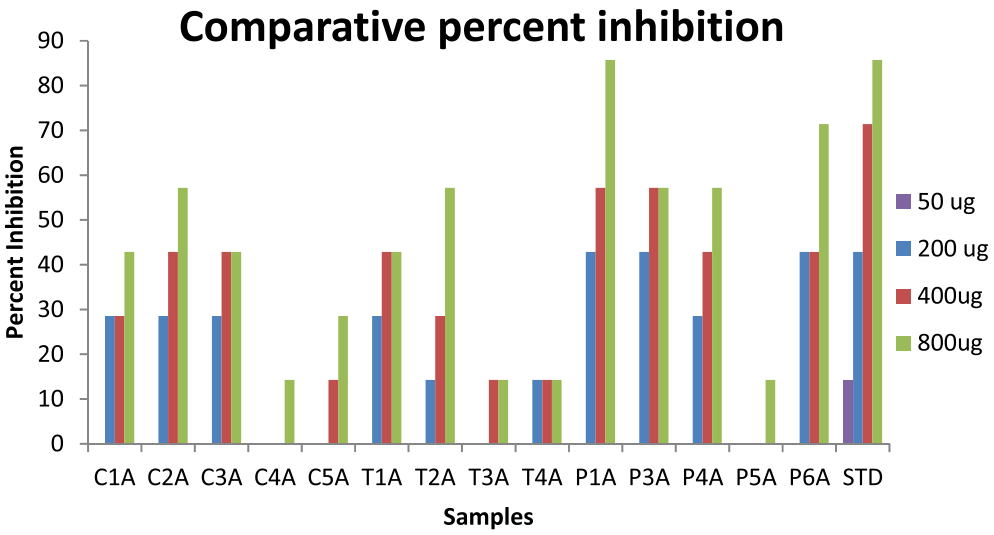


FIGURE 3 The comparative percent inhibition of compounds in an in vitro anti-inflammatory model

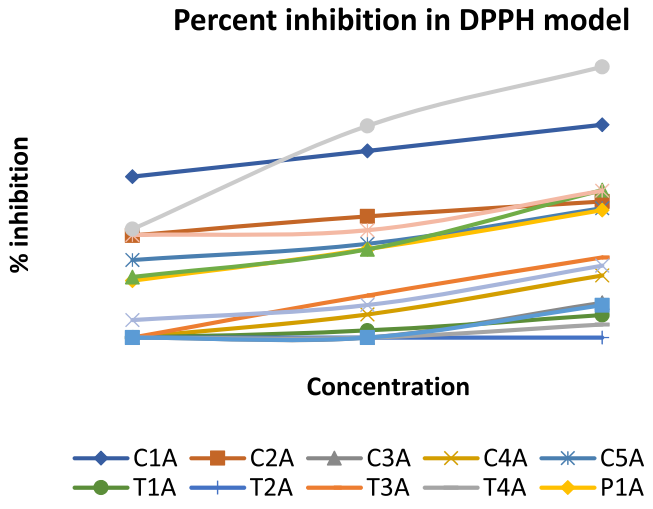


FIGURE 4 The percent inhibition of compounds in an in vitro antioxidant model

and time issues of drug development and discovery. Due to the inadequate drug likeness properties of many active agents with a significant biological activity, these compounds have failed in clinical trials.[29] On the basis of Lipinski's rule of five, the drug likeness properties were analyzed by ADME parameters using the Molinspiration online property calculation toolkit,[30] and data are summarized in Table 3.

All the compounds exhibited noteworthy values for the various parameters analyzed and showed good drug-like characteristics based on Lipinski's rule of five and its variants, which characterized these agents to be likely orally active. For the synthesized compound **6e**, the data obtained were within the range of accepted values. Parameters such as the number of rotatable bonds and total polar surface area are linked with the intestinal absorption; results showed that all synthesized compounds had good absorption. The in silico assessment of all the synthetic compounds has shown that they have very good pharmacokinetic properties, which are reflected in their physicochemical values, thus ultimately enhancing the pharmacological properties of these molecules.

3 | EXPERIMENTAL SECTION

All organic solvents were acquired from Poona Chemical Laboratory, Pune and Research-Lab Fine Chem Industries, Mumbai and were used as such without further purification. The melting points were measured on a DBK melting point apparatus and are uncorrected. Microwave irradiation was carried out in *Raga's* synthetic microwave oven. IR spectra were recorded on Shimadzu IR Affinity 1S (ATR) fourier transform infrared spectrophotometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Bruker Advance neo 500 spectrophotometers using tetramethylsilane as an internal standard, and $CDCl_3$ and dimethyl sulphoxide-d_6 as solvent and chemical shifts, respectively, were expressed as δ ppm units. Mass spectra were obtained on Waters quadrupole time-of-flight micromass (ESI-MS) mass spectrometer.

3.1 | General procedure for the synthesis of synthesize new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives (4a-d, 5a-f and 6a-e)

Conventional method: An equimolar amount of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-

TABLE 3 Pharmacokinetic parameters of (**4a-d**, **5a-f**, and **6a-e**) compounds

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski violation	Drug likeness model score
Rule	-	-	-	-	<500	≤5	<10	<5	≤1	-
4a	90.81	52.72	5	397.75	554.42	5.83	5	0	2	−0.68
4b	90.81	52.72	5	420.56	651.31	6.92	5	0	2	−0.84
4c	90.81	52.72	5	411.28	588.87	6.63	5	0	2	−0.25
4d	90.81	52.72	5	415.63	633.32	6.76	5	0	2	−0.56
5a	87.62	61.96	6	432.58	578.42	6.10	6	0	2	−0.46
5b	90.81	52.72	5	407.04	548.39	6.04	5	0	2	−0.80
5c	87.62	61.96	6	437.51	596.41	6.19	6	0	2	−0.22
5d	90.81	52.72	5	423.60	562.42	6.49	5	0	2	−0.51
5e	87.62	61.96	7	447.32	632.39	7.01	6	0	2	−0.45
5f	90.81	52.72	5	434.11	617.28	7.33	5	0	2	−0.36
6a	86.53	65.11	3	374.21	536.76	6.25	5	0	2	−0.53
6b	86.53	65.11	3	357.65	522.74	5.87	5	0	2	−0.36
6c	86.53	65.11	3	341.09	508.71	5.49	5	0	2	−0.32
6d	86.53	65.11	3	354.62	543.15	6.10	5	0	2	−0.93
6e	86.53	65.11	3	344.11	488.29	5.26	5	0	1	−0.81

Abbreviations: % ABS, percentage absorption; TPSA, topological polar surface area; n-ROTB, number of rotatable bonds; MV, molecular volume; MW, molecular weight; milogP, logarithm of partition coefficient of compound between n-octanol and water; n-ON acceptors, number of hydrogen bond acceptors; n-OHNH donors, number of hydrogen bonds donors.

one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) was taken in a round-bottom flask using glacial acetic acid (5 ml) as a solvent and were refluxed for the period of time indicated in Table 1. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction, the mixture was cooled and poured into ice-cold water. The obtained solid was filtered and washed with water and dried and purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

Ultrasound method: A mixture of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) in acetic acid (5 ml) was taken in a 50-ml round-bottom flask. The mixture was irradiated in the water bath of an ultrasonic cleaner at 35–40°C for a period of time indicated in Table 1. After completion of the reaction (monitored by TLC), the mixture was poured into ice-cold water, and the obtained solid was collected by simple filtration and washed successively with water. The crude product was purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

Microwave irradiation method: An equimolar amount of 2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3**) (0.002 mol) and substituted aldehydes (0.002 mol) was taken in a round-bottom flask (RBF) using glacial acetic acid (5 ml) as a solvent, and the contents of RBF were subjected to MW irradiation for the period of time indicated in Table 1 at 350 W. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was cooled and poured into ice-cold water. The obtained solid was filtered and washed with water and dried and purified by crystallization from ethyl acetate to obtain pure compounds (**4a-d**, **5a-f**, and **6a-e**).

3.1.1 | (4*E*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl) methylene)-1*H*-pyrazol-5(4*H*)-one (4a)

Orange solid; Wt. 930 mg, Yield 84%; IR(ν_{max}/cm^{-1}): 2,926 (=C—H), 1,681 (C=O), 1,598 (C=N), 1,519 (C=C), 1,234 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.35–7.91 (m, 8H, Ar—H), 8.11 (s, 1H, pyrazolyl-H), 10.10 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 161.4 (C=O), 151.7, 140.1, 137.8, 134.9, 131.1, 130.0, 129.6, 129.1,

128.70, 128.6, 119.7, 115.7, 113.5; MS (ESI-MS): *m/z* 555.01 $(M + H)^+$.

3.1.2 | (4*E*)-4-((3-(5-Bromothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl) methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4b)

Orange solid; Wt. 1.05 g; Yield 81%; IR (ν_{max}/cm^{-1}): 2,927 (=C—H), 1,680 (C=O), 1,598 (C=N), 1,516 (C=C), 1,231 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.16 (d, 1H, J = 3.50 Hz, Ar—H), 7.26–7.19 (m, 3H, Ar—H), 7.84 (dd, 2H, *J* = 5.00 Hz and 9.00 Hz, Ar—H), 8.10 (s, 1H, pyrazole-H), 10.11 (s, 1H, =C—H); MS: *m/z* 651.03 $(M + H)^+$.

3.1.3 | (4*E*)-4-((3-[5-Chlorothiophen-2-yl]-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4c)

Orange solid; Wt. 873 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 2,926 (=C—H), 1,682 (C=O), 1,597 (C=N), 1,518 (C=C), 1,232 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.07 (s, 1H, Ar—H), 7.26–7.18 (s, 1H, Ar—H), 7.44 (d, 1H, *J* = 6.00 Hz, Ar—H), 7.52 (m, 2H, Ar—H), 7.86 (d, 2H, *J* = 7.00 Hz, Ar—H), 8.11 (s, 1H, pyrazole-H), 10.16 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.4 (C=O), 151.3, 139.5, 138.3, 135.0, 133.5, 130.8, 130.0, 128.8, 127.6, 127.4, 120.0, 116.3, 114.6; MS: *m/z* 547.11 $(M + H)^+$.

3.1.4 | (4*E*)-4-((3-(5-Bromothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (4d)

Orange solid; Wt. 960 mg; Yield 76%; IR (ν_{max}/cm^{-1}): 2,926 (=C—H), 1,681 (C=O), 1,597 (C=N), 1,520 (C=C), 1,235 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.16 (d, 1H, *J* = 4.00 Hz, Ar—H), 7.21 (d, 1H, *J* = 3.50 Hz, Ar—H), 7.44 (t, 1H, *J* = 7.50 Hz, Ar—H), 7.52 (t, 2H, *J* = 7.50 Hz, Ar—H), 7.75–7.86 (d, 2H, *J* = 7.50 Hz, Ar—H), 8.47 (s, 1H, pyrazole-H), 10.16 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 183.2 (C=O), 162.3, 151.2, 143.2, 142.9, 139.4, 138.3, 134.9, 133.7, 133.4, 131.2, 130.6, 129.8, 129.1, 128.8, 128.5, 128.2, 120.6, 119.9, 119.6, 116.2, 115.9, 114.6; MS: *m/z* 633.05 (M + H).

3.1.5 | (4*Z*)-3-(Trifluoromethyl)-4-((3-[4-methoxyphenyl]-1-phenyl-1*H*-pyrazol-4-yl) methylene)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5a)

Orange solid; Wt. 971 mg; Yield 84%; IR (ν_{max}/cm^{-1}): 3,141 (=C—H), 1,703 (C=O), 1,595 (C=N), 1,514 (C=C), 1,224 (C—F); ^{1}H NMR spectrum, δ, ppm: 3.92 (s, 3H, —OCH_3), 7.10 (d, 2H, *J* = 8.50 Hz, Ar—H), 7.51 (t, 2H, *J* = 8.50 Hz, Ar—H), 7.62 (d, 2H, *J* = 8.50 Hz, Ar—H), 7.90 (d, 2H, *J* = 9.00 Hz, Ar—H), 7.99 (s, 1H, pyrazole-H), 10.19 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.5 (C=O), 161.1, 158.7, 143.3, 141.4, 138.6, 134.9, 130.7, 129.7, 128.5, 122.6, 120.1, 116.8, 114.7, 113.7, 55.5 (OCH_3); MS: *m/z* 579.21 $(M + H)^+$.

3.1.6 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-([1,3-diphenyl-1*H*-pyrazol-4-yl]methylene)-1H-pyrazol-5(4*H*)-one (5b)

Orange solid; Wt. 876 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 3,142 (=C—H), 1,701 (C=O), 1,595 (C=N), 1,510 (C=C), 1,223 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.42 (m, 1H, Ar—H), 7.52 (t, 2H, *J* = 7.50 Hz, Ar—H), 7.57–7.58 (m, 3H, Ar—H), 7.68 (dd, 2H, *J* = 7.50 and 2.00 Hz, Ar—H), 7.90 (d, 2H, *J* = 8.00 Hz, Ar—H), 8.00 (s, 1H, pyrazole-H), 10.22 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.5 (C=O), 158.8, 143.0, 141.2, 138.6, 134.9, 130.3, 129.9, 129.7, 129.4, 129.2, 128.6, 120.0, 116.8, 114.0; MS: *m/z* 549.19 $(M + H)^+$.

3.1.7 | (4*Z*)-4-((3-[2-Fluoro-4-methoxyphenyl]-1-phenyl-1*H*-pyrazol-4-yl) methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5c)

Orange solid; Wt. 1.06 g; Yield 82%; IR (ν_{max}/cm^{-1}): 3,145 (=C—H), 1,702 (C=O), 1,596(C=N), 1,512 (C=C), 1,221 (C—F); ^{1}H NMR spectrum, δ, ppm: 3.91 (s, 3H, —OCH_3), 6.82 (dd, 1H, *J* = 2.50 and 12.00 Hz, Ar—H), 6.91 (dd, 1H, *J* = 2.00 and 8.50 Hz, Ar—H), 7.42 (t, 1H, *J* = 7.50 Hz, Ar—H), 7.58–7.49 (m, 2H, Ar—H), 7.79 (d, 1H, *J* = 2.50 Hz, Ar—H), 7.88 (d, 2H, *J* = 7.50 Hz, Ar—H), 8.52 (s, 1H, pyrazole-H), 10.20 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.7 (C=O), 162.6, 162.5, 154.1, 141.2, 138.6, 134.7, 132.5, 129.7, 128.5, 120.0, 117.6, 113.9, 111.2, 110.3, 102.2, 102.0, 55.8 (OCH_3); MS: *m/z* 653.26 $(M + H)^+$.

3.1.8 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-([1-phenyl-3-p-tolyl-1*H*-pyrazol-4-yl]methylene)-1*H*-pyrazol-5(4*H*)-one (5d)

Orange solid; Wt. 887 mg; Yield 79%; IR (ν_{max}/cm^{-1}): 3,143 (=C—H), 1,701 (C=O), 1,594 (C=N), 1,511 (C=C), 1,220 (C—F); ^{1}H NMR spectrum, δ, ppm: 2.44 (s, 3H, —CH_3), 7.45 (d, 1H, J = 7.50 Hz, Ar—H), 7.51 (t, 1H, J = 7.50 Hz, Ar—H), 7.62 (d, 1H, J = 8.00 Hz, Ar—H), 7.65 (d, 1H, J = 8.00 Hz, Ar—H), 9.90 (s, 1H, pyrazole-H), 11.96 (s, 1H, =C—H); MS: m/z 563.08 $(M + H)^+$.

3.1.9 | (4*Z*)-3-(Trifluoromethyl)-1-(perfluorophenyl)-4-((1-phenyl-3-(4-[trifluoro methoxy]phenyl)-1*H*-pyrazol-4-yl)methylene)-1*H*-pyrazol-5(4*H*)-one (5e)

Orange solid; Wt. 960 mg; Yield 76%; IR (ν_{max}/cm^{-1}): 3,145 (=C—H), 1,700 (C=O), 1,595 (C=N), 1,517 (C=C), 1,225 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.42–7.44 (m, 3H, Ar—H), 7.51–7.54 (m, 2H, Ar—H), 7.71 (d, 1H, J = 2.00 Hz, Ar—H), 7.73 (d, 1H, J = 2.00 Hz, Ar—H), 7.88 (d, 1H, J = 2.00 Hz, Ar—H), 7.90 (d, 1H, J = 3.50 Hz, Ar—H), 7.92 (s, 1H, pyrazole-H), 10.21 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.4 (C=O), 157.3, 150.5, 143.2, 142.9, 140.3, 138.5, 134.9, 130.9, 129.8, 129.0, 128.7, 121.5, 120.6, 120.0, 118.4, 116.6, 114.4; MS: m/z 633.23 $(M + H)^+$.

3.1.10 | (4*Z*)-4-((3-[3,4-Dichlorophenyl]-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one (5f)

Orange solid; Wt. 1.03 g; Yield 84%; IR (ν_{max}/cm^{-1}): 3,144 (=C—H), 1,701 (C=O), 1,596 (C=N), 1,517 (C=C), 1,227 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.44 (m, 1H, Ar—H), 7.48 (d, 1H, J = 2.00 Hz, Ar—H), 7.50 (d, 1H, J = 2.00 Hz, Ar—H), 7.53 (d, 1H, J = 7.50 Hz, Ar—H), 7.67 (d, 1H, J = 8.50 Hz, Ar—H), 7.83 (d, 1H, J = 2.00 Hz, Ar—H), 7.87–7.89 (m, 2H, Ar—H), 7.89 (s, 1H, pyrazole-H), 10.18 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 162.3 (C=O), 156.1, 143.2, 142.9, 139.7, 138.4, 135.0, 134.5, 133.7, 131.2, 131.1, 130.3, 129.8, 128.8, 128.3, 120.0, 116.4, 114.7; MS: m/z 617.15 $(M + H)^+$.

3.1.11 | (*Z*)-4-([6-Chloro-5,7-dimethyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluoro phenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6a)

Orange solid; Wt. 900 mg; Yield 84%; IR (ν_{max}/cm^{-1}): 3,074 (=C—H), 1,707 (C=O), 1,666 (C=O), 1,624 (C=N), 1,508 (C=C), 1,192 (C—F); ^{1}H NMR spectrum, δ, ppm: 2.54 (s, 3H, —CH_3), 3.01 (s, 3H, —CH_3), 7.26 (s, 1H, Ar—H), 8.50 (s, 1H, chromone-H), 10.54 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 175.4 (C=O), 164.2 (C=O), 162.3, 155.1, 144.5, 143.4, 143.3, 139.7, 134.7, 120.9, 120.2, 119.4, 118.3, 118.2, 118.1, 22.2 (—CH_3), 18.6 (—CH_3); MS: m/z 537.11 $(M + H)^+$.

3.1.12 | (*Z*)-4-([6-Chloro-7-methyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluoro phenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6b)

Orange solid; Wt. 783 mg; Yield 75%; IR (ν_{max}/cm^{-1}): 3,076 (=C—H), 1,705 (C=O), 1,664 (C=O), 1,627 (C=N), 1,508 (C=C), 1,192 (C—F);^{1}H NMR spectrum, δ, ppm: 2.54 (s, 3H, —CH_3), 7.47 (s, 1H, Ar—H), 8.24 (s, 1H, Ar—H), 8.48 (s, 1H, chromone-H), 10.62 (s, 1H, =C—H); MS: m/z 523.08 $(M + H)^+$.

3.1.13 | (*Z*)-4-([6-Chloro-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6c)

Orange solid; Wt. 812 mg; Yield 80%; IR (ν_{max}/cm^{-1}): 3,074 (=C—H), 1,707 (C=O), 1,662 (C=O), 1,621 (C=N), 1,509 (C=C), 1,193 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.55 (d, 1H, J = 9.00 Hz, Ar—H), 7.73 (d, 1H, J = 2.50 and 9.00 Hz, Ar—H), 8.26 (d, 1H, J = 2.50 Hz, Ar—H), 8.47 (s, 1H, chromone-H), 10.63 (s, 1H, =C—H); MS: m/z 509.08 $(M + H)^+$.

3.1.14 | (*Z*)-4-([6,8-Dichloro-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6d)

Orange solid; Wt. 845 mg; Yield 78%; IR (ν_{max}/cm^{-1}): 3,078 (=C—H), 1,707 (C=O), 1,665 (C=O), 1,626 (C=N), 1,506 (C=C), 1,194 (C—F); ^{1}H NMR spectrum, δ, ppm: 7.83 (d, 1H, J = 2.50 Hz, Ar—H), 8.17 (d, 1H, J = 2.50 Hz, Ar—H), 8.40 (s, 1H, chromone-H), 10.66 (s, 1H, =C—H); MS: m/z 543.07 $(M + H)^+$.

3.1.15 | (*Z*)-4-([7-Methyl-4-oxo-4*H*-chromen-3-yl]methylene)-2-(perfluorophenyl)-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (6e)

Orange solid; Wt. 800 mg; Yield 82%; IR (ν_{max}/cm^{-1}): 3,076 (=C—H), 1,703 (C=O), 1,666 (C=O), 1,627 (C=N), 1,510 (C=C), 1,193 (C—F);^{1}H NMR spectrum, δ, ppm: 2.51 (s, 3H, —CH_3), 7.48 (d, 1H, J = 8.00 Hz, Ar—H), 7.60 (dd, 1H, J = 8.00 and 2.00 Hz, Ar—H), 8.08 (d,1H, J = 1.50 Hz), 8.54 (s, 1H, chromone-H), 10.64 (s, 1H, =C—H); ^{13}C NMR spectrum, δ_C, ppm: 174.5 (C=O), 165.5 (C=O), 162.4, 154.2, 143.4, 142.4, 137.5, 136.3, 126.2, 120.9, 123.3, 120.2, 118.6, 118.5, 118.2, 118.1, 21.1 (—CH_3); MS: m/z 489.14 $(M + H)^+$.

3.2 | Anti-inflammatory activity

All the synthesized compounds were screened for their in vitro anti-inflammatory activities against the standard drug diclofenac sodium. The minimum inhibitory concentration was determined by the well diffusion method at 1 mg/ml of concentration. (Table 2). A volume of 1 ml of diclofenac sodium at different concentrations (50, 100, 200, 400, 800, and 1,000 μg/ml) was homogenized with 1 ml of aqueous solution of bovine serum albumin (5%) and incubated at 27°C for 15 minutes. The mixture of distilled water and bismuth sulphite agar constituted the control tube. Denaturation of the proteins was caused by placing the mixture in a water bath for 10 minutes at 70°C. The mixture was cooled within the ambient room temperature, and the activity of each mixture was measured at 255 nm. Each test was conducted thrice. The following formula was used to calculated inhibition percentage:

$$\%\text{inhibition} = \text{absorbance of control} - \text{absorbance of sample} / \text{absorbance of control} \times 100.$$

3.3 | In silico ADME

In the present study, we have calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB), and Lipinski's rule of five[31] using the Molinspiration online property calculation toolkit.[30] Absorption (% ABS) was calculated by: % ABS = 109 − (0.345 × TPSA).[32] Drug likeness model score (a collective property of physicochemical properties, pharmacokinetics, and pharmacodynamics of a compound that is represented by a numerical value) was computed by MolSoft software.[33]

4 | CONCLUSIONS

In conclusion, we have constructed pyrazole and fluorine in one molecular framework as new 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives under conventional and nonconventional methods like microwave irradiation and ultrasonication, respectively, via Knoevenagel condensation and evaluated their biological activity. Ultrasonication and microwave irradiation can shorten the reaction time from a few hours to a few minutes and increases the product yield (74–84%) compared to the conventional method (59–75%). The synthesized compounds exhibited promising anti-inflammatory activity compared to the standard drug diclofenac sodium. Similarly, the synthesized compound displayed promising antioxidant activity compared to the standard drug. Furthermore, an analysis of the ADME parameters for synthesized compounds showed good drug-like properties and can be developed as an oral drug candidate, thus suggesting that compounds from the present series can be further optimized and developed as a lead molecule.

ACKNOWLEDGMENT

The authors are thankful to the Department of Science and Technology, New Delhi for providing research facilities under FIST scheme and to CIF, Savitribai Phule Pune University, Pune and SAIF, Panjab University, Chandigarh for providing spectral facilities.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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How to cite this article: Dengale SG, Akolkar HN, Karale BK, et al. Synthesis of 3-(trifluoromethyl)-1-(perfluorophenyl)-1*H*-pyrazol-5(4*H*)-one derivatives via Knoevenagel condensation and their biological evaluation. *J Chin Chem Soc.* 2020;1–12. https://doi.org/10.1002/jccs.202000357