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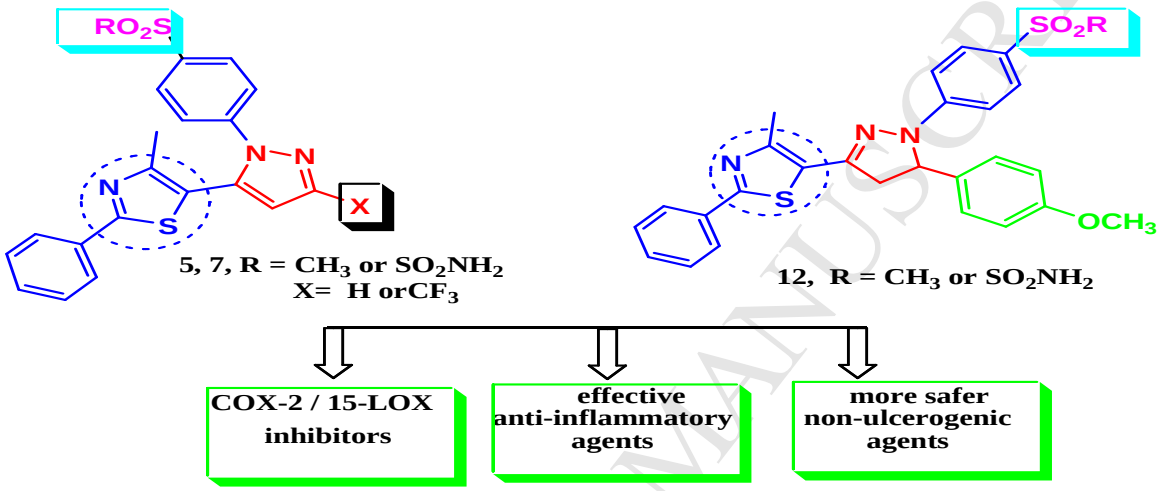
Graphical abstract



Synthesis of new thiazolo-celecoxib analogues as dual cyclooxygenase-2 / 15-lipoxygenase inhibitors: Determination of regio-specific different Pyrazole Cyclization by 2D NMR

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Abstract: Two new series of 1,5-diaryl pyrazoles (**5a**, **5b**, **7a**, **7b** and **10**) and 1,5-diaryl pyrazoline (**12a** and **12 b)** were prepared as both Cyclooxygenase-2 and 15-lipoxygenase inhibitors. Carrageenan-induced rat paw edema, ulcer index and anti-COX-1/ COX-2 and 15-LOX inhibition assays were also included. Cyclization of different pyrazoles was discussed using 2D NMR such as HSQC, HMBC and NOSEY determinations. Compound **5a** is more effective with ED_{50} = 0.98 and 3.98 µM against COX-2 and 15-lipoxygenase respectively, than the references celecoxib (1.54 µM) and meclofenamate sodium (5.64 µM).

Keywords: Cyclooxygenase inhibitors, celecoxib analogues, SO_2NH_2 pharmacophores, 15-Lipoxygenase inhibitors, anti-inflammatory, DMFDMA, Ethyl trifloroacetate.

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1. Introduction

Arachidonic acid (AA) is biologically transformed into a variety of inflammatory mediators through two metabolic pathways, cyclooxygenase and lipoxygenase. Cyclooxygenases are responsible for the production of Prostaglandins (PGs), thromboxanes (TXA_2) and prostacyclin (PGI_2) while lipoxygenases produce leukotrienes (LTs) and also catalyse the oxidation of lipoproteins (LDL, HDL) to atherogenic forms [1,2]. Cyclooxygenase isozymes are classed into a constitutive COX-1, induced COX-2 and COX-3 that still remain under investigation [3,4]. All the above-mentioned mediators are highly expressed in many inflammatory diseases, allergic reaction [5-7] and neo-angiogenesis [8,9]. The traditional non-steroidal anti-inflammatory drugs (NAISDs) such as aspirin or even the potent indomethacin exert their anti-inflammatory effect through rough inhibition of both COX-1 and 2. Reasonably, their action is associated with gastric bleeding due inhibition of constitutive COX-1. Moreover, selective COX-2 [10,11] inhibitors pronounced as Coxibs including celecoxib **I** (celebrex^{TM}) [12] (Fig.1), rofecoxib (vioxx^{TM}) or valdecoxib (bextra^{TM}) greatly inhibited the induced COX-2, but their administration is associated with myocardial thrombotic event and this is the reason of rofecoxib and valdecoxib withdrawal from the pharmaceutical market. Coxibs block the cyclooxygenase pathway, therefore metabolism of AA shunted to LOX pathway resulted in increasing the incidence of the unfavourable cardiovascular thrombotic event. According to the above findings, the development of new anti-inflammatory agent with a dual COX-2\LOX inhibition [13] activity, will introduce an effective cardio-safe drug with no ulcerogenic property. Celebrex is being a lead, due its high anti-inflammatory activity with a minimum gastrointestinal side effect. It has been belonged to a vicinal diaryl stelbene like structure with a pyrazole central ring and a sulfonamide (SO_2NH_2) at *p*- position of one of aryl groups. Also exploring many selective COX\LOX inhibitors such as darbufelone **II** and CI-987 (**III**) [14-16] (Fig.1), stated that they all have a thiazole moiety. So the aim of this research was directed to the synthesis of new celecoxib analogues on two designs (**IV** and **V**). The first design **IV** has three criteria that one of its diaryl was replaced with a thiazolyl moiety in order to maintain their COX-2\15-LOX inhibitory activities. Additional modification is adding or removing of CF_3 in position -3 of pyrazoles to investigate their essentiality for activity beside to keep both COX-2 inhibitory

pharmacophores (SO_2NH_2 or SO_2CH_3) as illustrated in Fig.1. Another design of compounds **V** which has three modifications. 1-one of aryl is replaced with the thiazole one. 2- keeping sulphonyl groups and 3- an electron rich group (OCH_3) was inserted as noticed in drabufelone **II** in order to maintain synergistic dual COX-2\15-LOX inhibitory activities. Herein, two new designs of highly effective drug hybrid (celecoxib/darbufelone) that might encourage the higher effectiveness of resulted compounds as anti-inflammatory agents with high safety profiles. Also, The dual inhibition of COX-2 / 15- LOX would decrease the cardiovascular adverse side effect. Accordingly and to a continuation of previous work [17-20], we synthesized and evaluate anti-inflammatory activity of the new targeted compounds. Moreover, *in vitro* COX-1/ 2 and 15-LOX inhibitory assays were done. Finally, the way of different pyrazole cyclization was discussed and proved by 2D NMR. These 2 D results has been converted the research to be a unique one, hence, many works of literature [21] prove their structures using theoretical computational studies without practical findings.

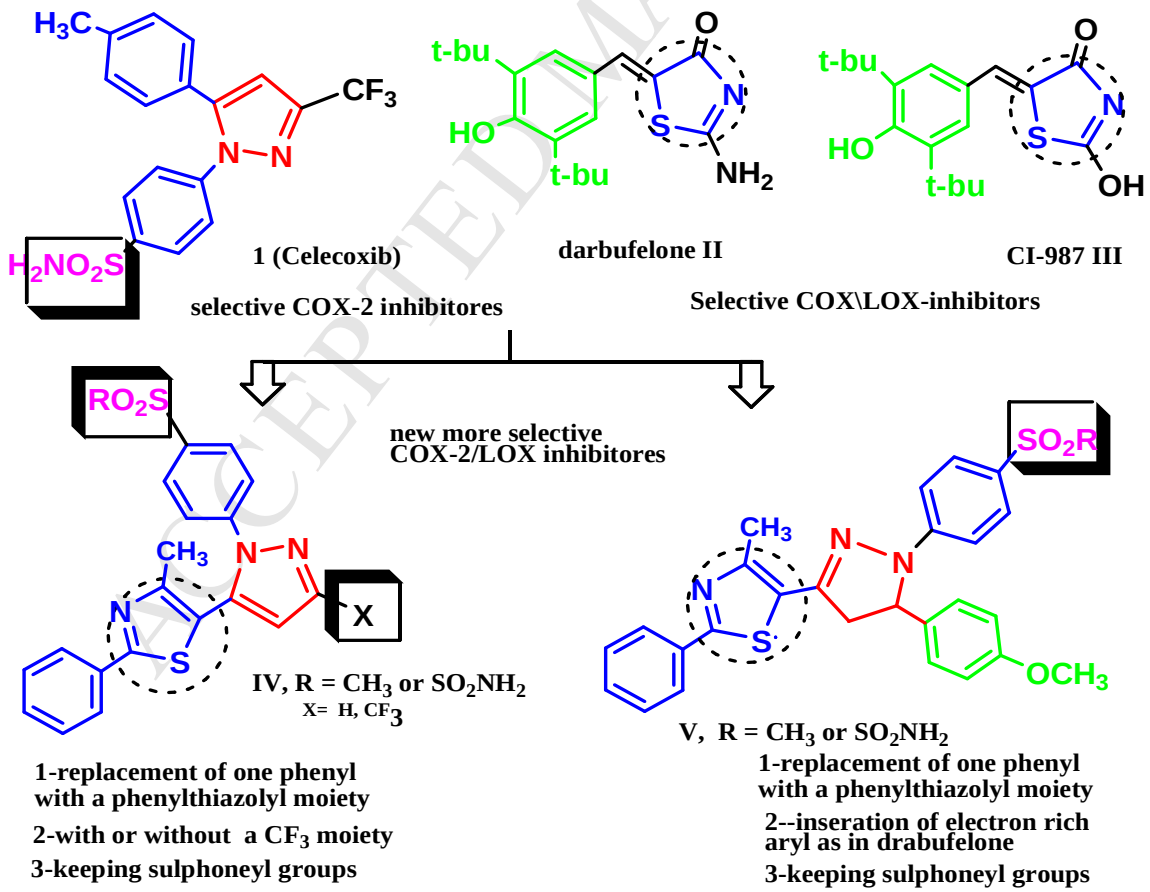
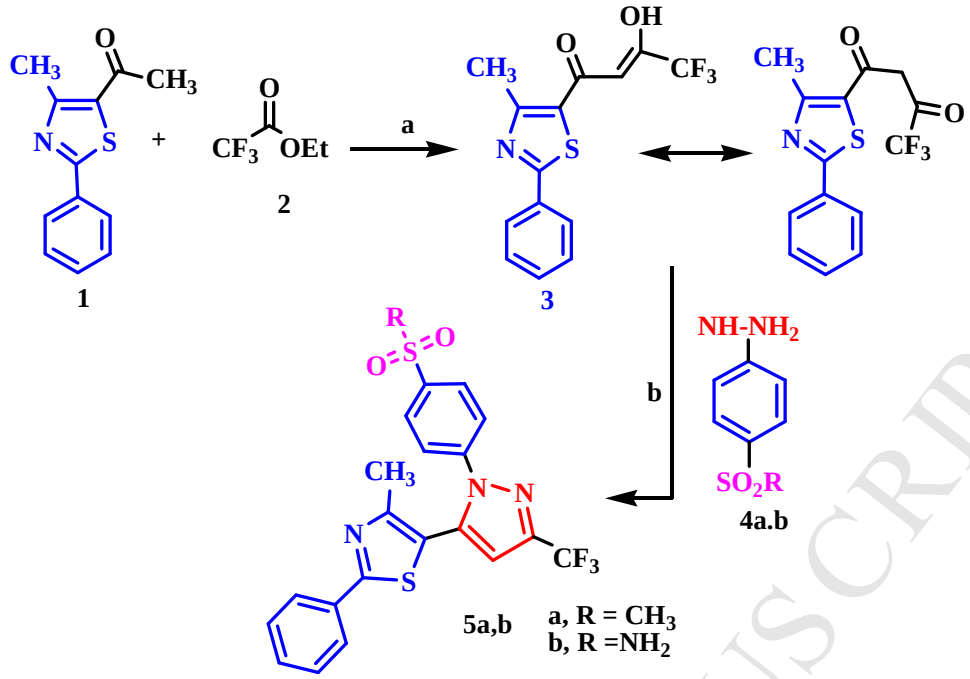


Fig 1: selective COX-2 inhibitors and selective COX \ LOX and Design of targeted compounds

2. Result and discussion

2.1. Chemistry

The Reaction of 1-(4-methyl-2-phenyl-thiazol-5-yl)-ethanone (**1**) with ethyl trifloroacetate under mixed Claisen condition resulted in the formation of β-diketo intermediate **3** which further cyclized with the use of un-symmetric hydrazines **4a** and/or **4b** [9,22,23] giving one and sole products **5a** or **5b** (scheme 1). Many reports stated about such reaction which constitutes the main synthetic approach for 1,5-di-substituted pyrazoles considered that either NH or NH_2 could start the attack to one carbonyl but which one of them?. In a way to answer such question, two possible forms of **5a** could be obtained either **A** or **B** (Fig.2) and definitely, the reaction is a region-specific one that one form **A** is predominantly formed. Many reports tried to explain their mechanism of formation and using quantum mechanics and computer programs to estimate which di-hydroxpyrazolidine intermediate **A** or **B** was energetically favoured and it is clearly obvious from this research findings that the favoured is intermediate **A**. Herein, we elucidate the structure of **5a** by the use of 2D HNMR (HMBC, HSQC, and NOESY) in order to discriminate between two forms **A** or B. NOESY spectrum of **5a** (R = CH_3) was achieved. Upon studying 3D of two possible forms of **5a** (**A** and **B**), the methyl protons of thiazole CH_3 showed two correlations on space. First, with C2-and C-6 H protons of methansulfonylphenyl hence, they are close in space in distance = 3.33, 3.88, 4.01 A^o and the other with the pyrazole H in distance = 3.88 A^o. Such interactions could be measured in NOSY experiment. From NOESY scan (on supplementary), we can identify a diagonal and a series of associated-off diagonal cross peaks. From these cross peaks, two peaks which are due to positive NOE signals for the concerned atoms confirming a vicinal diaryl structure **A** as the only formed compound while the other form **B** do not show these correlations.



Scheme1: synthesis of triflourodiketo-intermediate **3** and pyrazole derivatives **5a** and **5b.** Reagent and condition: (a) CH_3ONa, ethyl triflouroacetate, diethyl ether, (b) phenylhydrazine derivative, ethanol, 12h.

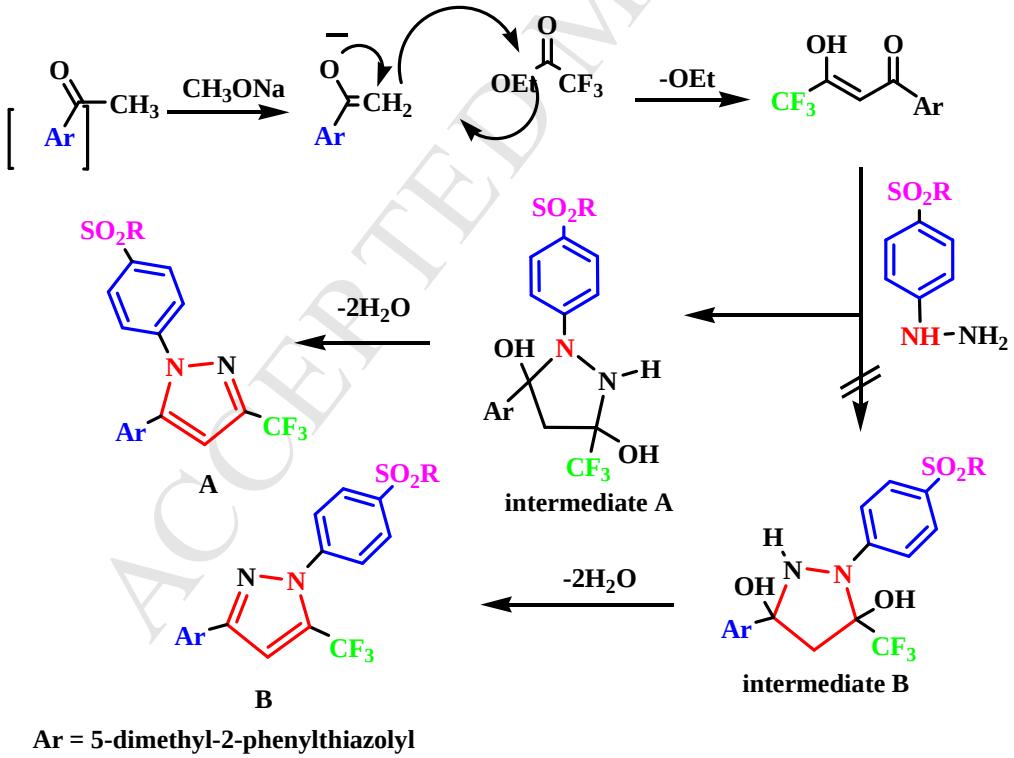
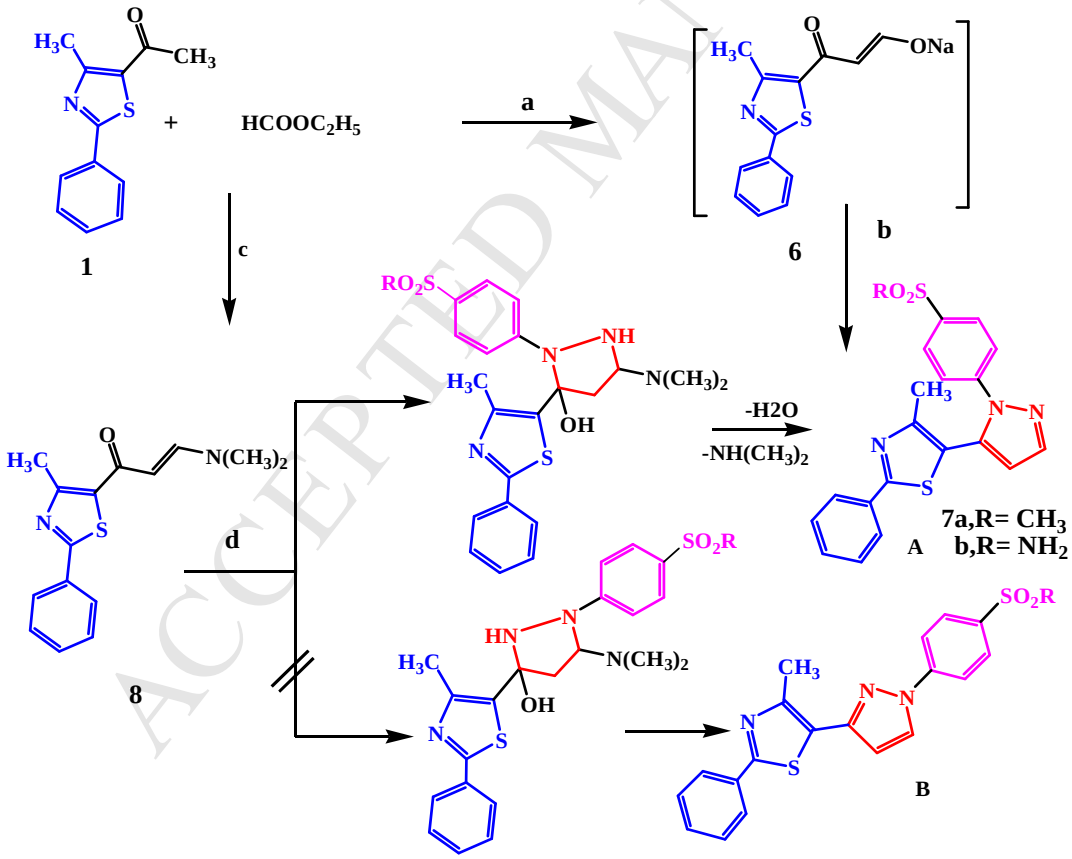


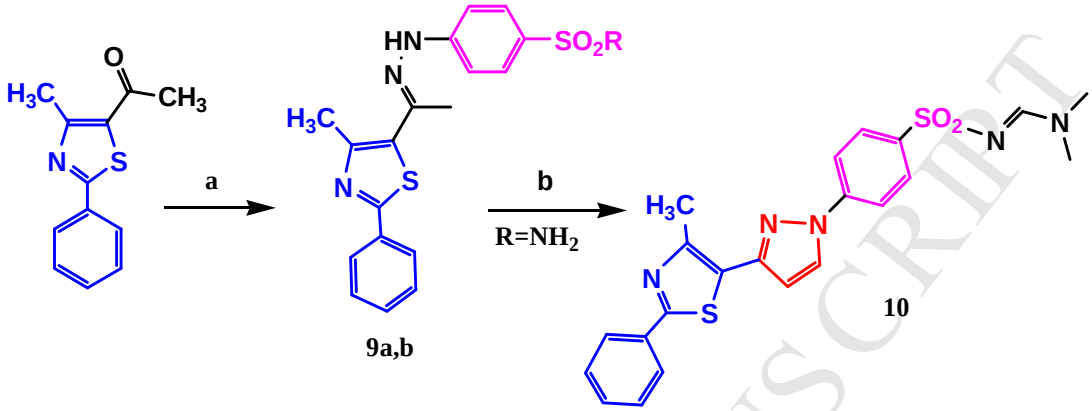
Fig.2: mechanism and possible forms of structures of **5a** and **5b**

Additionally, another pathway was adapted to get another pyrazoles **7a** and/or **7b**. Herein, these pyrazoles were prepared by two different methods. The first method, a green method involved the reaction of **1** with ethyl formate affording sodium salt of 3-hydroxy-1-(4-methyl-2-phenylthiazolyl-5-yl)prop-2-en-1-one (**6**) which in-situ reacted with respective phenylhydrazine in water as an eco-friendly solvent in the presence of a catalytic amount of acetic acid. The second method, it operated via formation of enaminone **8** which further reacted with phenylhydrazine **4a** or **4b** in ethanol to get the pyrazoles **7a** or **7b** (**Scheme 2**). Pyrazole **7a** structure was elucidated by all spectral data and using NOESY scan to prove **5a**. From the 3D of both forms of **7a** (**A** and **B**), the form **A** showed that the protons of thiazole CH_3 are in space with C2-and C-6 H protons of methanesulfonylphenyl in a distance = 3.3, 4.05 and 4.8 A^o and with pyrazole H-3 in distance = 3.2 A^o, such correlations could be measured in NOSY experiment while the form **B** do not show these correlations in space. Data of NOESY scan prove that the two aryls are vicinal to each other.



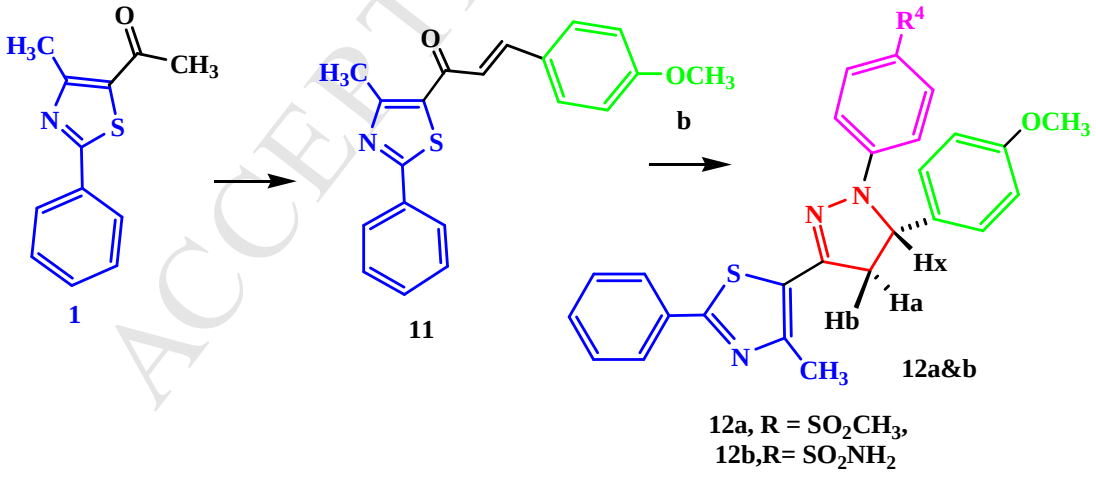
Scheme 2: synthesis of pyrazole derivatives **7a** and **7b**. Reagent and condition:(a) CH_3ONa, ethyl formate diethyl ether, (b) phenylhydrazine derivative, H_2O, AcOH, 1h. (C) DMFDMA, toluene, 12h., (d) phenylhydrazine derivative, AcOH, ethanol, 12h.

In a way to prepare compound **7** via another synthetic pathway, a trial was made through the formation of the hydrazone derivatives **9b** that reacted with DMFDMA in toluene that due to high acidic properties of SO_2NH_2 it reacted first then cyclization was completed giving the pyrazole derivative **10 (Scheme 3).**



Scheme 3: synthesis of hydrazones **9a** and **9b** and pyrazole **10**; Reagent and conditions (a) phenylhydrazine derivative HCl **4a** and **4b**, ethanol, (b) DMFDMA, toluene 24hr

Adapting Claisen –Schemidt condensation of the starting acetyl with 4-methoxy benzaldehyde, chalcone **11** was obtained that further cyclized with the substituted hydrazines **4a** or **4b** in boiling ethanol to the pyrazolines **12a or 12b** (**scheme 4**).



Scheme 4: Synthesis of chalcone **11** and pyrazolines **12a** and **12b**. Reagents and conditions: **(a)** 4-methoxybenzaldhyde, KOH, RT, 3-6 h; **(b)** *p*-substituted phenylhydrazine hydrochloride derivatives, EtOH, reflux and 8-12 h.

2.2. *Anti-inflammatory activity*

2.2.1. In vitro cyclooxygenase (COX) inhibition assay

The *in vitro* biological activity assay was operated to investigate the ability of synthesized compounds to inhibit both bovine COX-1 and COX-2. A colorimetric enzyme immunoassay (EIA) kit was used to screen the isozyme-specific inhibition [24]. Such COX assay is a time-saving tool for screening a vast no of inhibitors. The potency of testing compounds was determined as the concentration causing 50% enzyme inhibition (IC_{50}). Also, the COX-2 selectivity indexes (SI values) were calculated , is defined as IC_{50} (COX-1) / IC_{50} (COX-2) and compared with that of the standard drug celecoxib. All compounds were tested and the data obtained are listed in Table 1. For the COX-1 inhibition assay, pyrazoles **7a** and **7b** inhibit COX-1 in higher doses (10.30 and 9.80 µM, respectively) while pyrazoles **5a** and **5b** with a (CF_3) moiety inhibit COX-1 at doses (IC_{50} = 4.80 and 6.30 µM in sequent). Also, SI, for **7a** and **7b** (3.46, 4.39) don't differ so much from that of **5a** and **5b** and this may postulate that (CF_3) is not essential for reactivity. When compared **9a** to **9b**, compound **9a** inhibit COX-2 with (IC_{50} = 1.11 µM) that is more potent than **9b** (2.23 µM). This previous comparison concludes that SO_2CH_3 is more preferable than the other COX-2 pharmacophore (SO_2NH_2). Pyrazoline **12a** is the most active *in vitro* with SI = 5.08 which is higher than celecoxib its self with SI = 4.93. pyrazoline **12a** with a COX-2 inhibitors pharmacophore (SO_2CH_3) which maintain a higher lipid affinity with the highest partition coefficient (4.72) of all synthesized compounds. The other Most of the compounds showed moderate SI relative to the standard celecoxib that **5a**, **9a**, **9b**, **7b** showed SI = 4.89, 4.86, 4.39, 4.39 respectively. Pyrazole **5b** with (SO_2NH_2) pharmacophore, **10** which formed unexpectedly without a COX-2 pharmacophores and chalcone **11** which also without COX-2 pharmacophores were the least active compounds with a lower SI ~3.6.

2.2.2. *In vitro* lipoxygenase (LOX) inhibition assay

Different lipoxygenases such as (5, 8, 12, 15) are non-heme iron-containing dioxygenase that catalyze the addition of molecular oxygen to fatty acids containing *cis, sis* 1,4-pentadiene. The initial product of this reaction is 4-hydroxy-*cis, trans*-1,3-conjugated pentadienyl moiety. 15-LOX enzyme is designated from other LOXs that introduce hydroperoxide to lineolate and arachidonate substrates. Using the LOX enzyme assay kit [24] to measure the concentration of hydroxy peroxidase. The data obtained is listed in Table 1. (Clog P) values were calculated using (Chem. Draw

Ultra 3D, thremodynmic (octanol /Water) in a way to anticipate the lipoxygenase activity as whole most potent compounds showed reasonable higher liopxygenase inhibitory activity. Regarding 15-LOX inhibitory activity, compounds **5a** , **5b, 12a** were the most active as 15-LOX inhibitor with (IC_{50} = 3.98, 5.41 and 4.71 μM) compared that of meclofenamate sodium (IC_{50} = 5.64 μM) and also they nearly showed a higher partition coefficient (= 4.84, 4.72 and 4.72) from all synthesized compounds. From previous results (C-LogP**)** could be used as an indicator to anticipate liopoxygenase inhibitor potency. **12b**, **9a**, **7a**, **10** and **11** showed moderate inhibitory activity against 15-LOX enzyme in the range of (IC_{50}= 5.90-7.68 μM) while **9b** and **7b** have the lowest of the partition coefficient results (3.37, 3.79) and were the lowest as lipoxygenase inhibitors with (IC_{50} = 8.60 , 8.68 μM for both).

Table 1: *In vitro* COX-1, COX-2 inhibition, 15-Lox- and C-LogP of pyrazoles (**5a, 5b, 7a, 7b and 10**), hydrazones (**9a** , **9b**), Chalcone **11** and pyrazolines **(12a** , **12b)** and the reference drug celecoxib for COX and meclofenamte sodium for LOX.

Compound no	[a]COX-1 IC_{50} (μM)	[a]COX-2 IC_{50} (μM)	COX-1/ COX-2 S.I.[b]	[a]15-Lipoxygenase IC_{50}(μM)	[c]C-LogP
5a	4.80	0.98	4.89	3.98	4.84
5b	6.30	1.71	3.68	5.41	4.72
7a	10.30	2.97	3.46	7.49	3.92
7b	9.80	2.23	4.39	8.68	3.79
9a	5.40	1.11	4.86	6.35	2.98
9b	9.80	2.23	4.39	8.60	3.37
10	8.70	2.41	3.60	7.68	4.07
11	8.60	2.37	3.62	7.40	4.28
12a	5.80	1.14	5.08	4.71	4.72
12b	6.80	1.76	3.86	5.90	4.52
Celebrex	7.60	1.54	4.93	[d]ND	-

Aspirin	0.30	2.40	0.13	[d]ND	-
Meclofenamate sodium	[d]ND	[d]ND	[d]ND	5.64	-

[a] The *in vitro* test compound concentration required to produce 50% inhibition of COX-1 or COX-2. , soya bean 15 LOX assay kit, The result (IC_{50}, μM) is the mean of two determinations acquired using an ovine COX-1/ COX-2 assay Kits (Cayman Chemicals Inc., Ann Arbor, MI, USA) and the deviation from the mean is <10% of the mean value. [b] *In Vitro* COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}). [c]Clog, p partition coefficient calculated (octanol /Water) [D]ND = not determined.

2.2.3. *In vivo anti-inflammatory activity* [25,26]

The anti-inflammatory (AI) activities exhibited by the synthesized compounds were determined using a Carrageen-induced rat foot paw edema model and the percent in % edema inhibition was determined after 2and 4h and their relative potency of synthesized compounds to standard celecoxib was determined (Table 2). All synthesized compounds showed AI activity represented as a ratio relative to celecoxib with the range of 0.88-0.43. The most active compound was **5b** which is a trifluoropyrazole with a sulphonamide pharmacophore. Most of prepared pyrazoles showed good activity in order of **5b** > **5a**> **7b** > **10** > **7a**. On contrary to *in vitro* assays, AI activity stated that (SO_2NH_2) as a COX-2 pharmacophore was more effective than (SO_2CH_3). The methoxy chalcon **11** was active with a relative potency equal to 0.73 higher than the pyrazoline derivatives **12a** and **12b** those showing lower relative potencies (0.43 and 0.64 respectively). Pyrazolines **12a** and hydrazone **9a** were with the lowest AI as they showed the least relative potencies that conclude pyrazole is the preferred pharmacophores as they all showed good *in vivo* activities.

Table 2: *In vivo* anti-inflammatory activity of the tested compounds (orally administered) against Carrageenan-induced rat paw edema.

Compound no	Dose (mg/kg)	Increase in paw thickness (mm)		EIP %		[a]Relative potency	
		2h	4h	2h	4h	2h	4h
5a		0.29 ±0.013*	0.31±0.015*	53.23	51.56	0.89	0.79
5b		0.29 ±0.031*	0.27 ± 0.033*	53.22	57.81	0.89	0.88
7a		0.33 ±0.016*	0.33 ±0.017*	46.77	48.44	0.78	0.73
7b		0.28 ±0.012*	0.29 ±0.014*	54.84	54.69	0.92	0.83
9a		0.45 ± 0.026*	0.46 ±0.028*	27.42	28.13	0.46	0.43
9b		0.41±0.032*	0.39 ±0.034*	33.87	37.09	0.57	0.57
10		0.29 ±0.013*	0.31±0.015*	53.23	51.56	0.89	0.79
11	50	0.36 ±0.022*	0.34 ±0.023*	43.75	46.88	0.73	0.71
12a		0.45 ± 0.026*	0.46 ±0.028*	27.48	28.14	0.47	0.45
12b		0.39 ±0.024*	0.37 ± 0.025*	37.09	42.19	0.62	0.64
Control		0.62 ±0.017	0.64 ±0.019	0	0	-	-
Celecoxib	15	0.25 ±0.008*	0.22 ±0.01*	59.68	65.63	1	1

The results are expressed as means ± SEM (n = 5)Significance levels *p<0.05 as compared with the respective celecoxib. [a]Inhibitory activity in a carrageenan-induced rat paw edema assay. The results are expressed as the relative potency at 2 and 4 hours after oral administration of 50 mg/kg the test compound.

2.2.4. In vivo ulcerliability activity [27,28]

The ability of compounds to Ulcer formation was determined following oral dosing in rats (50mg/kg) as once daily for three consecutive days. Most of the tested compounds showed excellent activity (Table 3) when compared to reference where compounds **5a**, **5b**, **9b** and **7b** showed ulcer index = 2.78, 2.67, 2.65, 2.48 respectively and were safer than reference celecoxib (UI = 2.9) itself. Close to **7b** which is the safest compound of all synthesized compounds it belong to pyrazole series with a sulphonamide moiety and it would introduce a good safety profile drug. While the rest of the compound was close to celecoxib. Chalcone **11** which deviated from any sulphonamide pharmacophore, is the least safe one that showed the highest ulcer index (4.08).

Table 3: Ulcerogenic liability of the tested compounds following oral dosing in rats (50mg/kg) once daily for three consecutive days.

Comp.no	Average severity	Average no of ulcers	% incidence/10	Ulcer index
5a	0.18 ± 0.004***	0.6 ± 0.013***	2	2.78
5b	0.17 ±0.003***	0.5 ± 0.012***	2	2.67
7a	0 .85 ± 0.035***	0.5 ± 0.011***	3	4.35
7b	0.28 ± 0.015***	0.2 ± 0.007 ***	2	2.48
9a	0.57 ± 0.013**	0.3 ± 0.004***	3	3.87
9b	0.25± 0.008***	0.4 ± 0.006***	2	2.65
10	0.73 ± 0.017 ***	0.2 ± 0.004***	2	2.93
11	0.68 ± 0.02***	0.4 ± 0.008**	3	4.08
12a	0.53 ± 0.013**	0.3± 0.005 ***	3	3.83
12b	0.39±0.004***	0.4 ± 0.003***	3	3.79
Celecoxib	0.5 ± 0.013	0.4 ± 0.006	2	2.9
DMSO	0	0	0	0

Values represent means ± SEM for ten animals for each group.

Significance levels **p<0.01, ***p<0.001as compared with the respective celecoxib.

3. Conclusion

In this study, several thiazolo-celecoxib analogs (**5a, 5b, 7a, 7b**, **9a, 9b**, **10**, **12a, 12b**) were designed and prepared as dual cyclooxygenase and lipoxygenase inhibitors. All designed compounds are good inhibitors for such enzymes specially pyrazoline **12a** ((COX-1/COX-2) SI = 5.08 and IC_{50} = 4.70μM against Lipoxygenase) which is more selective than celecoxib and meclofenamate sodium references. Carrageenan-induced rat paw edema assay results showed that pyrazole **5a** is with the highest relative potency in comparison with celecoxib. UI liability showed a promising safety profile to most of the synthesized compounds.

4. Experimental protocols

4.1. Chemistry

All melting points were determined on a Griffin apparatus and were uncorrected. IR spectra were recorded on (Schimadzu IR 435) using KBr discs and values were

represented in cm^{-1}. ^{1}HNMR and ^{13}C were carried out on a spectrophotometer (Bruker 400 MHz) at the faculty of pharmacy, Beni-suef Univeristy, Beni-suef, Egypt. In DMSO-d_6 or $CDCl_3$ and D_2O using TMS as an internal standard, chemical shifts were recorded in ppm on δ scale, *J* (coupling constant) were estimated in hertz. The electron impact (EI) mass spectra were recorded on Hewlett 5988 spectrometer (Palo Alto, CA). Microanalysis was performed for C, H, N at Micro-analytical center, Cairo university, Cairo, Egypt and was ± 0.4% of theoretical values. Thin layer chromatography (TLC) silica gel plates were employed using a UV lamp to monitor the time of reaction and check the purity of products. Reagent and solvent used were of Aldrich (Milwaukee, WI) and used without further purification. Compounds **9** [18] and **11** [29] were prepared as previously reported procedures.

4.1.1. Synthesis of (Z)-1,1,1-Trifluoro-4-hydroxy-4-(4-methyl-2-phenylthiazol-5-yl)but-3-en-2-one (3)

A mixture of 1-(4-methyl-2-phenyl-thiazol-5-yl)-ethanone (**1**) (2.17 g, 0.01mol) and sodium methoxide (0.23 g / 5 mL methanol) in ether (15 mL) was stirred at room temperature for about 2 h. Ethyl trifloroacetate was added (1.42 g, 0.01 mol) was added and the reaction mixture was stirred at room temperature for 5 h. The resulting mixture was evaporated, then suspended in water and neutralized with acetic acid using PH meter to PH= 5.5 and, then extracted with ether. The ether extract was evaporated, then dried, and crystallized from ethyl acetate –methanol.

Yellow powder; Yield: 59%; mp: 260-262^{o}C; IR (KBr, cm^{-1}): 3423 (OH, broad band), 3060 (C-H aromatic), 2961 (C-H aliphatic), 1684 (C=O), 1623 (C=N); ^{1}H NMR(DMSO-d_6); δ 2.66 (s, 3H, CH_3 of thiazole), 5.68 (s, 1H, CHCO-CF_3), 7.46-4.52 (m, 3H, phenyl H-3, H-5, and H-4), 7.99 (t, 2H, phenyl H-2 and H-6 *J* = 2.4, 6.4 Hz,), OH (not appeared);

^{13}C NMR (DEPTQ); 18.17 ($CH_3$of thiazole), 90.82 (**C**H-$COCF_3$), 115.12, 118.02, 120.92, 123.83 [q] (CF_3); 126.99 (C3 and C5-phenyl); 129.67 (C2 and C6 phenyl); 130.99 (C4-phenyl); 133.21 (C-1 of phenyl); 136.06 (C5-of thiazole); 153.28 (C-4 of thiazole); 165.24 (C-2 of thiazole); 169.13, 169.41, 169.70, 169.98 [q] CF_3-C=O); 179.25 (HO-C=CH) ; MS (*m/z*,%): 313 [$(M)^{+\cdot}$, 1.3%], 43 [100%] ; Anal. Calcd. for $C_{14}H_{10}F_3NO_2S$: C, 53.67; H, 3.22; N, 4.47, Found: C, 53.21; H, 3.47; N, 4.59 %.

*4.1.2. General method for pyrazoles **5a** and **5b**:*

A solution of **3** (3.13 g, 0.01mol) and the corresponding phenyl hydrazine derivative (0.01 mol) in ethanol (30 mL) was refluxed for 10-12 h., (monitored by TLC). The solid separated on hot was filtered, dried, then crystallized from ethyl acetate-methanol

5-(Trifluoromethyl)-3-(4-methyl-2-phenylthiazol-5-yl)-1-(4-methyl-sulfonyl) phenyl)-1H-pyrazole (**5a**)

Yellow powder; Yield: 45%; mp: 190-192 ^{o}C; IR (KBr, cm^{-1}): 3013 (C-H aromatic), 2932 (C-H aliphatic), 1656 (C=N), 1389, 1130 (SO_2); ^{1}H NMR ($CDCl_3$); δ 2.26 (s, 3H, CH_3), 3.09 (s, 3H, SO_2CH_3), 6.89 (s, 1H, pyrazole H-4), 7.46-7.48 (m, 3H, phenyl H-3, H4, H-5), 7.65 (d, 2H, *J* = 8.4 Hz, methanesulfonyl phenyl H-2, H-6), 7.90-7.92 (m, 2H, phenyl H-2, H-6), 8.00 (d, 2H, *J* = 8.4 Hz, methanesulfonyl phenyl H-5, H-3); ^{13}C NMR (DEPTQ); 16.18 (thiazole CH_3), 44.49 (methansulfonyl CH_3) 109.25(C-4 pyrazole), (116.71,119.38, 122.06,124.74)[q] (CF_3), 117.04 (C-1 of methansulfonyl phenyl), 125,09 (C3,C5 of phenyl), 126.59 (C2, C6 of phenyl), 128.83 (C-2, C-6 methanesulfonyl phenyl), 129.15 (C-3,C-5 methanesulfonyl phenyl), 130.97 (C-5 of phenyl), 132.58 (C-1 of phenyl), 135.50 (C-4 of methanesulfonylphenyl phenyl), 140.35 (C-3 of pyrazole), 142.88(C-5 of thiazole),(143.90,144.28,144.67, 145.06) [q] (C-5 of pyrazole), 153.94 (C-4 of thiazole), 169.34 (C-2 of thiazole). (HMBC, HSQC and NOESY in supplementary materials, MS (*m/z*, %): 463 [(M) $^{+\cdot}$, 100 %], 465 [(M) $^{+\cdot}$ +2, 12.44 %]. Anal.Calcd.for $C_{21}H_{16}F_3N_3O_2S_2$: C, 54.42; H, 3.48; N, 9.07; Found: C, 54.17; H, 3.33; N, 9.05%.

*5-(Trifluoromethyl)-3-(4-methyl-2-phenylthiazol-5-yl)-1-(4-sulfamoyl-phenyl)-1H-pyrazole (**5b**).*

Yellow powder; Yield: 60%; mp: 300-302 ^{o}C; IR (KBr, cm^{-1}): 3381 (NH_2, broad band),3030 (C-H aromatic), 2926 (C-H aliphatic), 1668 (C=N), 1376, 1163 (SO_2);1H NMR (DMSO); δ 2.22 (s, 3H, CH_3), 7.44 (s, 1H, pyrazole H-4), 7.44-7.51 (m, 3H, phenyl H-3, H4, H-5), 7.53 (s, 2H, NH_2 (D_2O, exchangeable),7.66 (d, 2H, J = 8.4 Hz, methanesulfonylphenyl H-2, H-6), 7.87-7.89 (m, 2H, phenyl H-2, H-6), 7.91 (d, 2H, J = 8.4 Hz, methanesulfonylphenyl H-5, H-3); ^{13}C NMR (DEPTQ); 16. 49 (thiazole CH_3) , 109.28(C-4 pyrazole), (117.34,120.01,122.69,125.36) [q] (CF_3), 117.51 (C-1of sulfamoyl phenyl), 126.15 (C-3, C-5 of phenyl), 126.55 (C-2, C-6 of phenyl), 127.46 (C-2, C-6 of sulfamoyl phenyl), 129.88 (C-3, C-5 of sulfamoyl phenyl), 131.57 (C4- of phenyl), 132.30 (C-1 of phenyl), 135.5 (C-4 of sulfamoyl), 140.90

(C-3 of pyrazole), 143.9, 144.28, 144.67, 145.06 [q] (C-5 of pyrazole), 144.48 (C-5 of thiazole), 154.17 (C-4-of thiazole), 168.62 (C-2 of thiazole), MS (*m/z*,%): 464 [$(M)^{+\cdot}$, 97.86 %], 466 [$M^{+\cdot}$+2,12.25%], 105.08 [100%]. Anal. Calcd. for $C_{20}H_{15}F_3N_4O_2S_2$: C, 51.72; H, 3.26; N, 12.06 Found: C, 52.01; H, 3.33; N, 11.99%.)

*4.1.3 .General procedure for preparation of pyrazoles **7a** and **7b**.*

Method A: A mixture of **1** (2.17 g, 0.01mol) and sodium methoxide (0.54 g, 0.01mol) in ether 20mL and ethyl formate (0.74 g, 0.01mol) was stirred at room temperature for 3hr., the salt formed was filtered , dried and further reacted with hydrazines **4a** or **4b** (0.01mol) in water (30mL) and acetic acid (1.2 g, 0.02mol) and heated for 1hr and a solid formed, filtered and crystallized form ethanol / ethylacetate mixture (1:1).

Method B: a solution of enaminone **8** (2.72, 0.01mol) and substituted hydrazines (0.01mol) in ethanol was heated for 12hr., the reaction mixture was evaporated, dried and crystallized.

5-(4-Methyl-2-phenylthiazol-5-yl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole 7a: Yellow cubes ; Yield: 44%; mp: 177-179 ^{o}C; IR (KBr, cm^{-1}): 3058 (C-H aromatic), 2932 (C-H aliphatic), 1656 (C=N), 1360, 1199 (SO_2);^{1}H NMR ($CDCl_3$); δ 2.25 (s, 3H, CH_3), 3.08 (s, 3H, SO_2CH_3), 6.65 (d, 1H, *J* = 2.0 Hz, pyrazole H-4), 7.45-7.49 (m, 3H, phenyl H-3, H4, H-5), 7.62 (d, 2H, *J* = 8.8 Hz, methanesulfonylphenyl H-2, H-6), 7.85 (d, 1H, *J* = 2.0 Hz, pyrazole H-5), 7.92-7.95 (m, 2H, phenyl H-2, H-6), 7.96 (d, 2H, *J* = 8.8 Hz, methanesulfonylphenyl H-5, H-3); ^{13}C NMR (DEPTQ) ; 16.17 (thiazole CH_3), 44.54 (methansulfonyl CH_3) 112.01 (C-4 pyrazole), 118.91 (C-1of methansulfonylphenyl), 124.37 (C3,C5 phenyl), 126.62 (C2, C6 of phenyl), 128.67 (C-2, C-6 methanesulfonylphenyl), 128.79 (C-3, C-5 methanesulfonyl phenyl), 130.88(C-5 of phenyl), 132.51(C-1 of phenyl), 139.12 (C-4 of methanesulfonyl phenyl), 140.27(C-3 of pyrazole), 141.65(C-5 of pyrazole), 143.78 (C-5 of thiazole), 152.73 (C-4 of thiazole), 168.74(C-2 of thiazole). (NOESY in supplementary materials); MS (m/z,%): 395 [$(M)^{+\cdot}$, 100%], 397[$M^{+\cdot}$+2,18.73%]; Anal.Calcd.for $C_{20}H_{17}N_3O_2S_2$: C, 60.74; H, 4.33; N, 10.62; Found: C, 60.50; H, 4.30; N, 10.25%.

*5-(4-Methyl-2-phenylthiazol-5-yl)-1-(4-(sulfamoyl)phenyl)-1H-pyrazole **7b**:*

Yellow cubes; Yield: 60%; mp: 202-204 ^{o}C; IR (KBr, cm^{-1}): 3431,3307 (NH_2,), 3184 (C-H aromatic), 3030 (C-H aliphatic), 1594 (C=N), 1376, 1148 (SO_2); ^{1}H NMR ($CDCl_3$); δ 2.26 (s, 3H, CH_3), 5.02 (s, 2H, NH_2 (D_2O, exchangeable), 6.65 (d, 1H, *J* = 1.6 Hz, pyrazole H-4), 7.45-752 (m, 3H, phenyl H-3, H4, H-5), 7.53 (d, 2H, J = 8.4 Hz, sulfamoylphenylH-2, H-6), 7.85 (d, 1H, *J* = 1.6 Hz, pyrazole H-5), 7.92-7.97 (m, 4H, phenyl H-2, H-6 and sulfamoyl phenyl H-5, H-3); ^{13}C NMR (DEPTQ) ; 15.88 (thiazole CH_3), 111.80 (C-4 pyrazole), 119.08 (C-1of sulfamoyl phenyl), 124.26 (C3, C5 phenyl), 126.67 (C2, C6 of phenyl), 127.76 (C-2, C-6 sulfamoylphenyl), 129.16 (C-3, C-5 sulfamoyl phenyl), 130.95 (C-5 of phenyl), 132.33(C-1 of phenyl), 133.01 (C-4 of sulfamoyl phenyl), 140.05 (C-3 of pyrazole), 140.91 (C-5 of pyrazole), 142.75 (C-5 of thiazole), 152.50 (C-4 of thiazole),168.72 (C-2 of thiazole). MS (m/z,%): 396 [(M)+., 100%], 398 [$M^{+\cdot}$+2,13.53%]. Anal. Calcd. For $C_{19}H_{16}N_4O_2S_2$: C, 57.56; H, 4.07; N, 14.13; Found: C, 57.50; H, 4.03; N, 14.05%.

*4.1.4. General procedure for synthesis of **9a** and **9b***

A solution of **1** (2.17 g, 0.01mol) and the corresponding phenyl hydrazine derivative (0.01 mol) in ethanol (30 mL) containing a catalytic amount of acetic acid and heated under reflux for 3 h., (monitored by TLC). The solid separated on hot was filtered, dried,then crystallized from ethanol \ dimethyformamide mixture (5:1).

(E)-1-(1-(4-methyl-2-phenylthiazol-5-yl)ethylidene)-2-(4-methylsulfonyl)phenyl) hydrazine (9a)

Yellow Needles; Yield: 80%; mp: 204-206 ^{o}C; IR (KBr, cm^{-1}): 3597 (NH hydrazono), 3164, 3082 (C-H aromatic), 2938 (C-H aliphatic), 1593 (C=N), 1381, 1137 (SO_2); ^{1}H NMR (DMSO-d_6); δ 2.40 (s, 3H, CH_3), 2.66 (s, 3H, CH_3-C=N) 3.16 (s, 3H, SO_2CH_3), 7.34 (d, 2H, *J* = 8.4 Hz , H-2, H-6 of methanesulfonylphenyl),7.49-7.42 (m, 3H, phenyl H-3, H-4, H-5), 7.75 (d, 2H, *J* = 8.4 Hz, methanesulfonylphenyl H-3, H-5), 7.92-7.93 (m, 2H, phenyl H-2, H-6), 10.04 (s, 1H, NH (D_2O exchangeable); ^{13}C NMR (DEPTQ); 17.10 (CH_3, thiazole), 18.82 ($\underline{C}H_3$-C=N), 49.06 (CH_3, methanesulfonyl) 112.78 (C-2, C-6 methanesulfonylphenyl), 126,34 (C3, C5 of methansulfonylphenyl), 129.20 (C3, C5 of phenyl), 129.71 (C2, C6- of phenyl), 130.47 (C-5 of phenyl) ,130.70 (C-1 of methanesulfonylphenyl), 133.34 (C=NH-), 133.37 (C-1 of phenyl), 149.82 (C-4 of methanesulfonylphenyl), 149.88 (C-5 of thiazole), 150.15 (C-4 of thiazole), 163.57(C-2 of thiazole). MS (m/z,%): 385 [(M)$^{+\cdot}$,

100%], 387[$M^{+\cdot}$+2, 14.28 %] Anal.Calcd. for $C_{19}H_{19}N_3O_2S_2$: C, 59.20; H, 4.97; N, 10.90, Found: C, 59.01; H, 4.63; N, 10.85%.

*(E)-1-(1-(4-Methyl-2-phenylthiazol-5-yl)ethylidene)-2-(4-sulfamoyl-phenyl) hydrazine (**9b**).*

Yellow powder; Yield: 84%; mp: 275-277 ^{o}C; IR (KBr, cm^{-1}): 3382, 3300 (NH, NH_2), 3184 (C-H aromatic), 2936 (C-H aliphatic), 1592 (C=N), 1342, 1156 (SO_2); ^{1}H-NMR (DMSO-d_6); δ 2.38 (s, 3H, CH_3), 2.66 (s, 3H, CH_3-C=N), 7.11(s, 2H, NH_2) 7.28 (d, 2H, *J* = 8.4 Hz, H-2, H-6 of sulfamoylphenyl), 7.50 (3H, phenyl H-3, H-4, H-5), 7.67 (d, 2H, *J* = 8.4 Hz, sulfamoylphenyl H-3, H-5), 7.94 (m, 2H, phenyl H-2, H-6), 9.90 (s, 1H, NH (D_2O exchangeable). ^{13}C NMR (DEPTQ); 16.98 (CH_3, thiazole), 18.75 ($\underline{C}H_3$-C=N), 112.78 (C-2, C-6 sulfamoylphenyl), 126,34 (C3, C5 of sulfamoyl phenyl), 129.20 (C3, C5 of phenyl), 129.70 (C-2, C-6 of phenyl), 130.66 (C-4 of phenyl), 133.35 (C-1of sulfamoylphenyl), 133.54 (C=NH-), 134.43 (C-1 of phenyl), 138.95 (C-4 of sulfamoyl phenyl), 148.46 (C-5 of thiazole), 149.86 (C-4 of thiazole), 163.40 (C-2 of thiazole); 386 [$(M)^{+\cdot}$, 100%]. Anal. Calcd. for $C_{18}H_{18}N_4O_2S_2$: C, 55.94; H, 4.69; N, 14.50; Found: C, 56.01; H, 4.63; N, 14.25%.

*4.1.5. Synthesis 5-(4-Methyl-2-phenylthiazol-5-yl)-1-(4-(N,N-dimethylformamidine-sulfam oyl) phenyl) - 1H-pyrazole (**10**).*

A solution of **9b** (0.38 g, 0.001mol) and DMFDMA (0.03 mol) in toluene (30 mL) was heated under reflux for 24 h., (monitored by TLC). The reaction mixture is evaporated solid separated , dried then separated by preparative T.L.C as **10** as Off white powder ; Yield: 39 %; mp: 175-177 ^{o}C; IR (KBr, cm^{-1}): 2990 (C-H aromatic), 2933 (C-H aliphatic), 1590 (C=N), 1344, 1133 (SO_2); ^{1}H NMR (DMSO-d_6); δ 2.15 (s, 3H, thiazole CH_3), 2.90 (s, 3H, =N-CH_3), 3.1(s, 3H, =NCH_3), 6.84(d, 1H, *J* = 2.0 Hz, pyrazole H-4), 7.49-7.53 (m, 5H, phenyl H-3, H4, H5 and H2, H-6 of sulfomylphenyl H-2, H-6), 7.82 (d, 2H, *J* = 8.8 Hz, sulfamoylphenyl H-5, H-3), 7.87-7.90 (m, 2H, phenyl H-2, H-6), 7.93 (d, 1H, *J* = 2.0 Hz, pyrazole H-5), 8.21 (s, 1H, olfenic H); ^{13}C NMR (DEPTQ); 16.24 (thiazole CH_3), 35.59 (=NCH_3), 40.48 (=NCH_3), 111.95(C-4 pyrazole), 118.91 (C-1 of sulfamoylphenyl), 124.99 (C3, C5 phenyl), 126.51 (C2, C6 of phenyl), 127.65 (C-2, C-6 sulfamoylphenyl), 129.82 (C-3, C-5 sulfamoylphenyl), 131.25 (C-5 of phenyl), 132.51(C-1 of phenyl), 139.12 (C-4 of ulfamoylphenyl), 141.81(C-3 of pyrazole), 141.86(C-5 of pyrazole), 142.48(C-5 of thiazole), 152.98(C-4 of thiazole), 160.37 (olfenic CH), 168.74 (C-2 of thiazole). (

HMBC, HSQC in supplementary materials), MS (m/z, %): 467 [$(M)^{+\cdot}$, 1.76%], 71 [100%]. Anal.Calcd.for $C_{22}H_{21}N_5O_2S_2$: C, 58.52; H, 4.69; N, 15.51; Found: C, 58.77; H, 4.99; N, 15.75%.

*4.1.6. General procedure of pyrazolines **12a** and **12b***

*(S)-4,5-Dihydro-5-(4-Methoxyphenyl)-3-(4-methyl-2-phenylthiazol-5-yl)-1-(4-(methylsulfonyl)phenyl)-1H-pyrazole (**12a**)*

A solution of chalcone **11** (0.01 mol) and the corresponding phenyl hydrazine derivative (0.01 mol) in absolute ethanol (30 mL) was refluxed for 8-12 h., (monitored by TLC). The solid separated on hot was filtered, dried, then crystallized from ethanol/ethyl acetate mixture (1:1).

Yellow powder; Yield: 60 %; mp: 230-232; IR (KBr, cm^{-1}): 3013 (C-H aromatic), 2932 (C-H aliphatic), 1591 (C=N), 1324, 1164 (SO_2); ^{1}H NMR (DMSO-d_6); δ 2.51 (s, 3H, thiazole CH_3), 3.08 (s, 3H, OCH_3), 3.20 (dd, 1H, H_a, J_{ab} = 17.2 Hz, J_{ax}= 5.2 Hz), 3.72(s, 3H, SO_2CH_3), 4.10 (dd, 1H, H_b, J_{ab} = 17.2 Hz , J_{bx}= 12 Hz), 5.62(dd, 1H, H_x, J_{bx}= 12 Hz, J_{ax} = 5.2 Hz), 6.92 (d, 2H, J = 8.8 Hz methoxyphenyl H3, H5), 7.07 (d, 2H, methoxyphenyl H2, H6), 7.21 (d, 2H, J = 8.8 Hz, H-2, H-6 of sulfamoylphenyl), 7.50-7.51 (m, 3H, phenyl H-3, H-4, H-5), 7.52 (d, 2H, J = 8.8 Hz, sulfamoylphenyl H-3, H-5), 7.67-7.69 (m, 2H, phenyl H-2, H-6),). ^{13}C NMR(DEPTQ); 17.84 (CH_3, thiazole), 44.54 (OCH_3), 49.06 (CH_2 of pyrazoline), 55.45 (SO_2CH_3), 62.65 (CH of pyrazoline), 112.77 (C-2, C-6 methoxyphenyl), 115.02 (C3, C5 of methoxy phenyl), 125.26 (C1 of methoxyphenyl), 126.61 (C3, C5 of phenyl), 127.56 (C-3, C-5 of methanesulfonyl), 129.03 (C-2, C-6 of methanesulfonylphenyl), 129.81 (C-2, C-6 of phenyl), 131.15(C-5 of phenyl), 132.98 (C-1 of methanesulfanylphenyl), 133.41(C-1 of phenyl),145.2 (C-4 of methanesulfonyl phenyl and C3 of pyrazoline), 147.05 (C4-of methoxyphenyl), 153.15 (C-5 of thiazole), 159.24 (C-4 of thiazole), 165.46 (C-2 of thiazole). MS (m/z,%): 503 [$(M)^{+\cdot}$, 100%], Anal.Calcd.for $C_{27}H_{25}N_3O_3S_2$: C, 64.39; H, 5.00; N, 8.34, Found: C, 64.77; H, 5.30; N, 8.75%.

*(S)-4,5-Dihydro-5-(4-methoxyphenyl)-3-(4-methyl-2-phenylthiazol-5-yl)-1-(4-(sulfamoyl)phenyl)-1H-pyrazole **(12b).***

Yellow powder; Yield: 74%; MP: 273-275 ^{o}C; IR (KBr, cm^{-1}): 3335, 3318 (NH_2), 3118 (C-H aromatic), 2952 (C-H aliphatic), 1592 (C=N), 1369, 1159 (SO_2);

1H-NMR (DMSO-d_6); δ 2.64 (s, 3H, CH_3), 3.18 (dd, 1H, H_a, J_{ab} = 18 Hz, J_{ax}= 5.2 Hz), 3.71 (s, 3H, OCH_3), 4.10 (dd, 1H, H_b J_{ab} = 18 Hz, J_{bx}= 12.8), 5.62 (dd, 1H, H_x, J_{bx}= 12.8 Hz, J_{ax} = 5.2 Hz) 6.91 (d, 2H, *J* = 8.8 Hz methoxyphenyl H3, H5), 7.02-7.05 (m, 4H, methoxyphenyl H2, H6 and NH_2, D_2O exchangeable), 7.20 (d, 2H, *J* = 8.8 Hz, H-2, H-6 of sulfamoylphenyl), 7.51-7.52 (m, 3H, phenyl H-3, H-4, H-5), 7.61 (d, 2H, *J* = 8.8 Hz, sulfamoylphenyl H-3, H-5), 7.95-7.97 (m, 2H, phenyl H-2, H-6). ^{13}C NMR (DEPTQ); 17.80 (CH_3, thiazole), 45.44 (CH_2 of pyrazoline), 55.53 (OCH_3), 62.73 (CH of pyrazoline), 112.63 (C-2, C-6 methoxyphenyl), 114.95 (C3, C5 of methoxy phenyl), 125.1 (C1 of methoxyphenyl), 126.57 (C3, C5 of phenyl), 127.59 (C-3, C-5 of sufamoylphenyl), 133.01 (C-2, C-6 of sulfamoylphenyl), 133.01 (C-2, C-6 of phenyl), 132.98 (C-1of sulfamoylphenyl), 133.76 (C-5 of phenyl), 133.88 (C-1 of phenyl), 145.2 (C-4 of sulfamoyl phenyl), 144.34 (C4-of methoxyphenyl), 145.86 (C1 of sulfamoyl phenyl and C3 of pyrazoline), 152.80 (C-5 of thiazole), 159.27 (C-4 of thiazole), 165.24 (C-2 of thiazole). MS (m/z,%): 504 [$(M)^{+\cdot}$, 59.05%], 121.11 [100%]. Anal. Calcd. for $C_{26}H_{24}N_4O_3S_2$: C, 61.88,; H, 4.79; N, 11.10., Found: C, 61.64; H, 4.43; N, 11.24%.

4.2. Biological activity

4.2.1. In vitro cyclooxygenase (COX) inhibition assay

The ability of the test compounds listed in Table 1 to inhibit ovine COX-1 and COX-2 (IC_{50} value, μM) was determined using an enzyme immune assay (EIA) kit (Cayman Chemical, Ann Arbor, MI, USA) according to a previously reported methods.

4.2.2. In vitro 15-lipoxygenase (LOX) inhibition assay

The ability of the test compounds listed in Table 1 to inhibit soya bean 15-LOX (IC_{50} value, μM) and 15-LOX was determined using an enzyme immune assay (EIA) kit (catalogue no 760709, Cayman Chemical, Ann Arbor, MI, USA). Stock solutions were freshly prepared before use and buffer solution used (0.1 M Tris HCl, PH, 7.4). 10 µl of different compound were prepared in dissolved at the least amount of DMSO and diluted with the stock solution to be in concentrations of (0.001, 01, 1, 5, 10 µM) in a final volume of 210µl. And IC_{50} of test compounds were determined according to a manufacturer's instructions as reported methods.

4.2.3. *In vivo anti-inflammatory activity*

Animals**:** Adult male wister albino rats (100 – 150 g) were used in the pharmacological studies. The animals (five per cage) were maintained under standard laboratory conditions (light period of 12 h/day and temperature 27 ± 2° C), with access to food and water. The experimental procedures were carried out in strict compliance with the Institutional Animal Ethics Committee regulations. All experiments were performed in the morning, according to the guidelines for the care of laboratory animals. Carragenan-induced paw edema test**:** Anti-inflammatory activity of ten compounds, was evaluated by employing carragenan induced rat paw edema model according to a previously reported method after oral administration of a dose 50mg\kg of test compounds. % Inhibition in edema thickness was determined after 2h and 4h. % Relative potency after 2h and 4h was calculated in relation to standard celecoxib.

4.2.4. Ulcerogenic liability

Ulcerogenic liability of 15 compounds, which showed *in-vivo* anti-inflammatory activity, was evaluated according to the reported standard method. Rats were fasted for 18 hours before drug administration and classified into separate groups (5 rats per group). All treatments were administered *via* the oral route. The first group received 10% DMSO aqueous solution (v/v) and kept as control, the second group received celecoxib in ED_{50} (30.9 μmol / kg), while the other groups received the tested compounds dissolved in DMSO in ED_{50}.Treatment was continued once daily for 3 successive days in all groups. One hour after the last dose, the animals were sacrificed under general anesthesia and the stomach was removed, opened along the greater curvature and rinsed with saline. The gastric mucosa was examined with a magnifying lens (10 xs) for the presence of lesions in the form of haemorrhages or linear breaks and erosions. The ulcer index was calculated and the degree of ulcerogenic effect was expressed in terms of: i) percentage incidence of ulcer divided by 10, ii) average number of ulcers per stomach, and iii) average severity of ulcers. The ulcer index is the value that resulted from the sum of the above three values.

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- New thiazolo-celecoxib analogues were designed and synthesized.
- Thiazolo-celecoxib drug hybrid showed higher COX-2 / 15-LOX inhibition properties.
- Designed compounds were evaluated as anti-inflammatory activity using Carrageenan-induced rat paw edema and proved activity.
- Ulcer liability index of compounds was determined and they showed higher safety profiles.
- Most of the compounds were effective as anti-inflammatory and more selective towards COX-2 /15-LOX.