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Research Article

MOLECULAR DOCKING, SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF SOME TETRASUBSTITUTED THIOPHENE DERIVATIVES

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ABSTRACT

A series of novel 4-amino-5-(4-oxo-3-aryl-3,4-dihydroquinazolin-2-yl)-2 (arylamino)thiophene-3-carbonitrile (7a-7j) were synthesized, characterized and evaluated for anti-inflammatory activity. Compounds 7e and 7h show % protection 45.34 % and 47.25 % respectively against carrageenan induced rat paw edema model whereas diclofenac sodium show 60.60 % after 4 hour at dose 20mg/kg. 7a, 7b, 7c, 7d, 7f, 7g, 7i and 7j show mild to moderate anti-inflammatory activity. Molecular docking experiments were carried on COX2 enzyme (pdb code: 1CX2) to identify potential COX2 inhibitor. The results indicate that 7a show lowest binding energy -9.32 kcal/mol with hydrogen bond interaction with ARG 120 and PRO 84 in comparison with reference compound SC 558 having binding energy -7.49 kcal/mol. Compounds 7e, 7g and 7h were found to have minimum binding energy -8.34, -9.59 and -7.79 kcal/mol respectively. The docking results revealed that compound has good affinity with COX2 binding site.

Keywords: Molecular docking, COX2, Tetrasubstituted thiophene, Anti-inflammatory activity.

INTRODUCTION

Inflammation is a local tissue reaction in response to noxious stimuli such as chemicals, pathogens, thermal and mechanical injuries. It is characterized by heat, swelling, redness and pain. Inflammatory mediators such as histamine, 5-hydroxytryptamine, bradykinin, leukotrienes, prostaglandins are responsible to cause inflammation. Prostaglandins are synthesized from cyclooxygenase (COX) which exist in two isoforms, COX1 (constitutive form) and COX2 (inducible form). Non steroidal anti-inflammatory drugs (NSAID) are most widely used therapeutic agents in treatment of inflammation, pain and arthritis. NSAID inhibit action of COX and thereby inhibiting prostaglandin synthesis[1-3]. However there are undesirable side effects due to long term usage of NSAID such as gastrointestinal bleeding, gastric ulceration & nephrotoxicity[4-6]. Although a great deal of progress has been made toward developing novel anti-inflammatory agents, design and development of a safe, effective and economical therapy for treating inflammatory conditions still presents a major challenge. Therefore there is need to develop novel anti-inflammatory agent which is safer and do not show side effects. Thiophene heterocycle is of particular importance in medicinal chemistry because it shows wide array of biological activities such as antimicrobial[7-8,13], antitubercular[9], analgesic[5], antiinflammatroy[4], anticancer[10-11], antiprotozoal[12]. Hence the aim of present research was to synthesize novel tetrasubstituted thiophene compounds and evaluation for their anti-inflammatory activity.

EXPERIMENTAL

Chemistry

All Melting points were determined by open tube capillary method and are uncorrected. IR spectra (KBr) of compounds were measured on Shimadzu 8400S and absorption bands are expressed in cm^{-1}. ^1H NMR spectra were recorded on Bruker 500 MHz spectrometer with $CDCl_3$ as the solvent. TMS was used as the internal standard for NMR. Mass spectra were recorded on Bruker. All the reactions were monitored by thin layer chromatography using pre-coated aluminium plates with silica gel 60 F254 to check purity.

General procedure for synthesis of 4-amino-5-(4-oxo-3-aryl-3,4-dihydroquinazolin-2-yl)-2-(arylamino)thiophene-3-carbonitrile (7a-7j)

To a solution of malononitrile (5) (1.0 mmol, 1 equiv.) in dimethyl formamide (3 mL) dried potassium carbonate (1.0 mmol,1 equiv) aryl isothiocyanate (1.0 mmol,1 equiv.) was added and the mixture was stirred for 1 hr at room temperature. Then quinazolinone (1.0 mmol,1 equiv.) (4) was added, reaction mixture was heated for 1 hr. The reaction was quenched with 10 mL water. The crude product (7) precipitated and was purified by filtration followed by crystallization in methanol.

2-(p-tolylamino)-4-amino-5-(3,4-dihydro-4-oxo-3-phenylquinazolin-2-yl)thiophene-3-carbonitrile (7a)

Yield: 46.80 %; m.p. : 290-292˚C; I.R. (KBr, cm $^{-1}$): 3477 (N-H), 3068 (C-H s aromatic), 2208 (CN), 1681 (C=O), 1444 (C=C aromatic), 754 (C-H b aromatic); ^{1}H NMR (300 MHz,$CDCl_3$)δ(ppm): 1.5 (s,3H,CH_3), 6.5-8.3 (m,14H, aromatic), 3.9 (2H,NH_2); HR-MS, m/z (M+1): 450.13.

2-(4-chlorophenylamino)-4-amino-5-(3,4-dihydro-4-oxo-3-p-tolylquinazolin-2-yl)thiophene-3-carbonitrile (7b)

Yield: 58.40 %; m.p. : 258-260˚C; I.R. (KBr, cm $^{-1}$): 3329 (N-H), 3010 (C-H s aromatic), 2200 (CN), 1730 (C=O), 1606 (C=C aromatic), 719 (C-H b aromatic); ^{1}H NMR (300 MHz,$CDCl_3$)δ(ppm): 2.48 (3H,CH_3), 6.4-7.9 (m,13H, aromatic), 3.9 (2H,NH_2); HR-MS, m/z (M+1): 484.09.

2-(4-chlorophenylamino)-4-amino-5-(3,4-dihydro-4-oxo-3-phenylquinazolin-2-yl)thiophene-3-carbonitrile (7c)

Yield: 63.35 %; m.p. : 256-258˚C; I.R. (KBr, cm $^{-1}$): 3367 (N-H), 3034 (C-H s aromatic), 2210 (CN), 1687 (C=O), 758 (C-H b aromatic); ^{1}H NMR (300 MHz,$CDCl_3$)δ(ppm): 6.7-7.8 (m,14H, aromatic), 3.9 (2H,NH_2); HR-MS, m/z (M+1): 469.16

2-(4-methoxyphenylamino)-4-amino-5-(3-(2-chlorophenyl)-3,4-dihydro-4-oxoquinazolin-2-yl)thiophene-3-carbonitrile (7d)

Yield: 62.04 %; m.p. : 236-238˚C; I.R. (KBr, cm $^{-1}$): 3448 (N-H), 3010 (C-H s aromatic), 2200 (CN), 1687 (C=O), 1448 (C=C aromatic)721 (C-H b aromatic); ^{1}H NMR (300 MHz,$CDCl_3$)δ(ppm): 3.87 (3H,OCH_3), 7.1-7.9 (m,13H, aromatic), 3.9 (2H,NH_2); HR-MS, m/z (M+1): 500.09.

4-amino-5-(3-(2-chlorophenyl)-3,4-dihydro-4-oxoquinazolin-2-yl)-2(phenylamino)thiophene-3-carbonitrile (7e)

Yield: 54.76 %; m.p. : 268-270˚C; I.R. (KBr, cm $^{-1}$): 3277 (N-H), 3068 (C-H s aromatic), 2202 (CN), 1670 (C=O), 1456 (C=C aromatic),744 (C-H b aromatic); ^{1}H NMR (300 MHz,$CDCl_3$)δ(ppm): 7.1-7.7 (m,14H, aromatic), 3.9 (2H,NH_2), HR-MS, m/z (M+1): 470.08.

4-amino-5-(3,4-dihydro-3-(2-methoxyphenyl)-4-oxoquinazolin-2-yl)-2-(phenylamino)thiophene-3-carbonitrile (7f)

Yield: 56.33 %; m.p. : 271-273˚C; I.R. (KBr, cm $^{-1}$): 3354 (N-H), 3061 (C-H s aromatic), 2198 (CN), 1680 (C=O), 1510 (C=C aromatic),754 (C-H b aromatic); ^{1}H NMR (300 MHz,$CDCl_3$)δ(ppm): 3.80 (3H,OCH_3), 6.9-7.7 (m,16H, aromatic); HR-MS, m/z (M+1): 466.13.

2-(p-tolylamino)-4-amino-5-(3-(4-bromophenyl)-3,4-dihydro-4-oxoquinazolin-2-yl)thiophene-3-carbonitrile (7g)

Yield: 47.89 %; m.p. : 289-291˚C; I.R. (KBr, cm $^{-1}$): 3340 (N-H), 3053 (C-H s aromatic), 2204 (CN), 1680 (C=O), 1585 (C=C aromatic),771 (C-H b aromatic); ^{1}H NMR (300 MHz,$CDCl_3$)δ(ppm): 3.41 (3H,CH_3), 7.1-8.3 (m,13H, aromatic), 3.9 (2H,NH_2); HR-MS, m/z (M+1): 530.04.

2-(p-tolylamino)-4-amino-5-(pyridin-4-yl)thiophene-3-carbonitrile (7h)

Yield: 45.04 %; m.p. : 230-232˚C; I.R. (KBr, cm $^{-1}$): 3313 (N-H), 3041 (C-H s aromatic), 2274 (CN), 1656 (C=O), 1450 (C=C aromatic),705 (C-H b aromatic); ^{1}H NMR (300 MHz,$CDCl_3$)δ(ppm): 2.13 (3H,CH_3), 6.9-8.6 (m,11H, aromatic); HR-MS, m/z (M+1): 307.10

2-(4-methoxyphenylamino)-4-amino-5-(pyridin-4-yl)thiophene-3-carbonitrile (7i)

Yield: 41.02 %; m.p. : 138-140˚C; I.R. (KBr, cm $^{-1}$): 3254 (N-H), 3090 (C-H s aromatic), 2202 (CN), 1670 (C=O), 810 (C-H b aromatic); ^{1}H NMR (300 MHz,$CDCl_3$)δ(ppm): 3.8 (3H,OCH_3), 6.3-8.6 (m,11H, aromatic),HR-MS, m/z (M+1): 323.12

4-amino-2-(phenylamino)-5-(quinolin-2-yl)thiophene-3-carbonitrile (7j)

Yield: 54.43 %; m.p. : 232-234˚C; I.R. (KBr, cm $^{-1}$): 3279 (N-H), 3026 (C-H s aromatic), 2285(CN), 1728 (C=O), 1469 (C=C aromatic),759 (C-H b aromatic); ^{1}H NMR (300 MHz,$CDCl_3$)δ(ppm): 6.8-7.9 (m,14H, aromatic); HR-MS, m/z (M+1): 343.10.

Anti-inflammatory activity

Carrageenan induced rat paw edema method

Synthesized compounds were evaluated for *in-vivo* anti-inflammatory activity using carrageenan induced rat paw edema model[19]. Wistar albino rats weighing between 180 to 220 gm of either sex were divided into ten groups containing six animals in each group (one control, one standard, eight test groups). Test compounds and standard drug diclofenac sodium suspended in 0.5 % CMC were administered orally in a dose of 20mg/kg. One hour post dosing 0.1ml of 1% carrageenan in normal saline was injected into subplantar region of right hind paw of each rat to induce edema. Paw volume of rat was measured using plethysmometer at 1h, 2h, 3h, 4h, 5h and 6h time interval. All the experimental protocols were approved by institutional animal ethical committee (approval no. DYPIPSR/IAEC/17-18/P-27) and experiments were conducted in accordance with standard guidelines. The % protection in paw volume was calculated according to the following formula:

$$\% \text{ Inhibition} = Vc\text{-}Vt/Vc \times 100$$

Where Vc paw volume of control, Vt paw volume of test compound.

Molecular docking

To understand mechanism of antiinflammatory activity of synthesized compounds and to identify lead compound, molecular docking study was performed using Autodock Tools 1.5.6. The energies of the interaction in different conformations were compared to determine best fit.

Preparation of ligand

The ligands (tetrasubstituted thiophene) were studied for their binding activities into COX2 enzymes. Chemical structures of ligands were drawn in ChemDraw Ultra 8.0 software, 3dimensional structures constructed using Marvin View and were saved in mol format. The energies were minimized for low iteration using convergent method with 0.01 kcal/mole. The

number of torsion angles were set for each ligand. The prepared ligands were used as input files for AutoDock tool[4] which determine rotatable bonds of ligand to be able to generate different conformers for the docking. Ligands were saved as PDBQT.

Preparation of protein

Macromolecules from protein data bank was used as anti-inflammatory drug target. X-ray crystal structure of COX2 in complex with co-crystallised ligand SC558 (PDB code: 1CX2)[6,14] was downloaded from protein data bank (http://www.rcsb.org). Co-crystallised ligand, water molecules and hereroatom were deleted from protein. In AutoDock Tools all polar hydrogens and atomic Gastiger charges were added and saved as PDBQT.

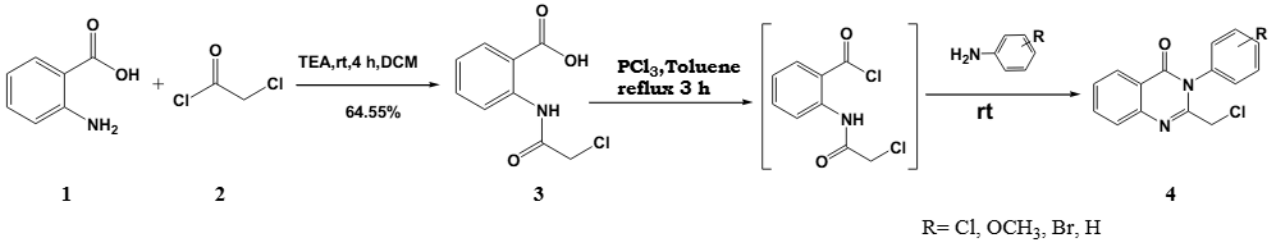
Grid generation and Docking

Grid maps were calculated with autogrid program available in Autodock server to study binding energies between ligand and receptor protein. Around the binding site of co-crystallised ligand, a grid box with dimension of 60×60×60 Å size (X,Y,Z) with a spacing of 0.375 Å was created using autodock tool. A separate grid parameter file was generated for each ligand. The centre of the grid box was set at co-crystallised ligand centre and grid energy calculations were carried out. After preparation of input files (ligand and protein) the Lamarckian genetic algorithm method was implemented for docking simulation. After successful docking of inhibitors into the catalytic site of COX enzymes, autodock docking calculation was done using default parameters and ten docked conformations were generated for each compound. The energy of binding interactions was estimated using genetic algorithm.

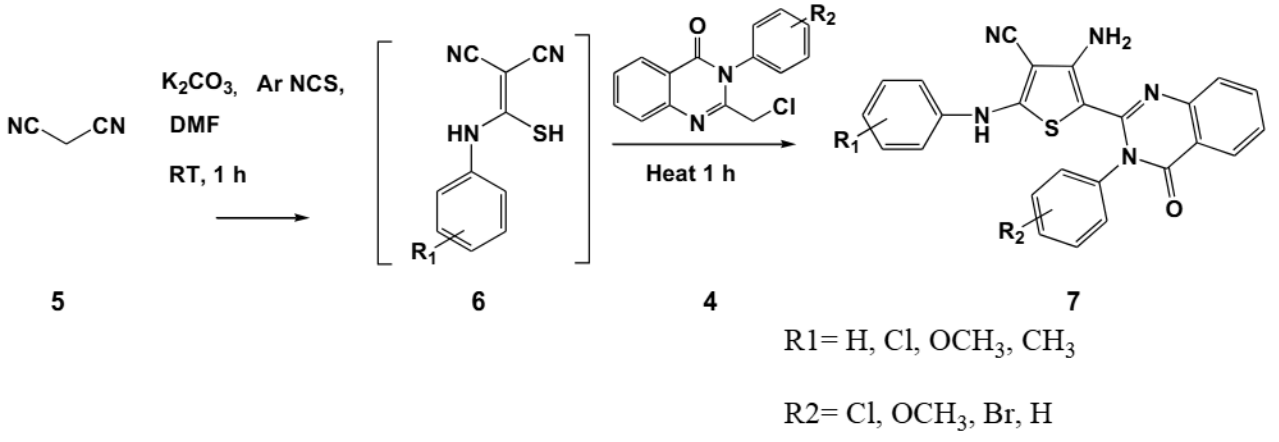
RESULT AND DISCUSSION

Chemistry

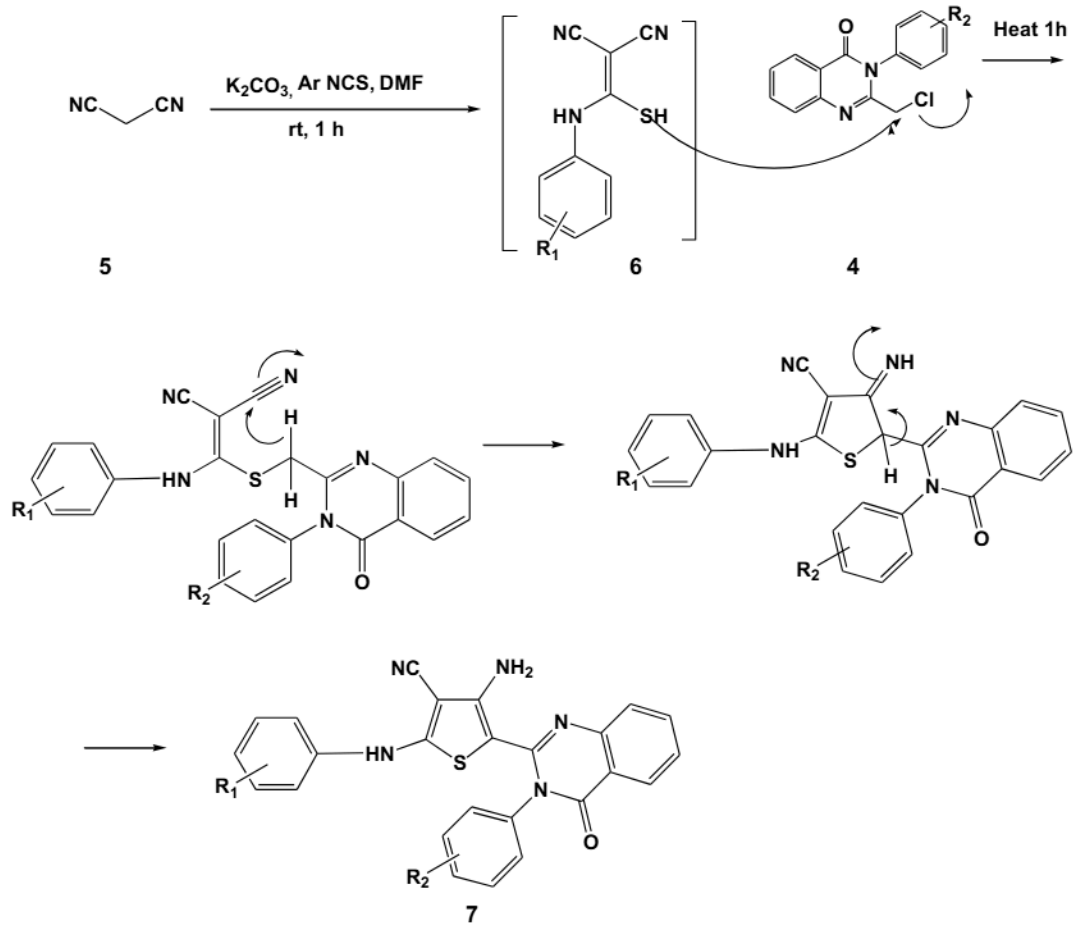
Different derivatives of tetrasubstituted thiophene from malononitrile were prepared by following one pot synthesis. Initially intermediate compounds 2-chloro methyl-3– aryl-3H-quinazolinone-4-one were synthesized by using modified Niementowski synthesis as per reported procedure[15] as outlined in scheme 1. For target compound synthesis (7) starting material were malononitrile (5) , aryl isothiocyanate and 2-chloro methyl-3– aryl-3H-quinazolinone-4-one (4). In first step malononitrile undergo condensation with aryl isothiocyanates to yield N,S ketene acetal (6)[16-18] stirring 1 hr at room temperature in presence of potassium carbonate using DMF as solvent. Further in same reaction mixture one equivalent of quinazolinone (4) was added and reaction mixture was heated for 1 hour. The tetrasubstituted thiophene was obtained by quenching DMF with water and the product was filtered and recrystallized from methanol or purified by column chromatography with n-hexane : ethyl acetate (40 %) as mobile phase. The title compounds (7a-7j) were prepared using synthetic strategy depicted in scheme 2 and mechanism shown in scheme 3.



Scheme 1: Synthetic route for 2-chloro methyl-3– aryl-3H-quinazolinone-4-one

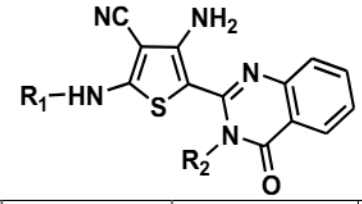


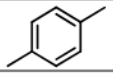
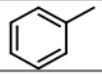
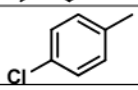
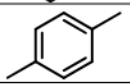
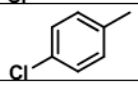
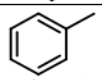
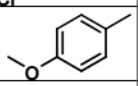
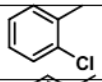
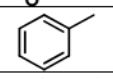
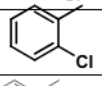
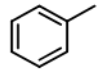
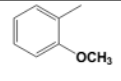
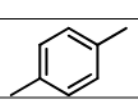
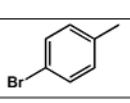
Scheme 2: Synthesis of title compounds (7a-7j)

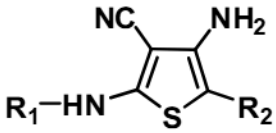


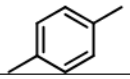
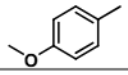
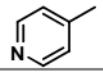
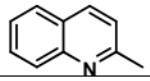
Scheme 3: Possible mechanism for synthesis of target compound

Table 1. Physicochemical data of newly synthesized compounds 7a-7j



Compounds	R_1	R_2	Molecular formula	Molecular wt	Melting Point °C	% Yield
7a			C26H19N5OS	449.53	290-292	46.80
7b			C26H18ClN5OS	483.97	258-260	58.40
7c			C25H16ClN5OS	469.95	256-258	63.35
7d			C26H18ClN5O2S	499.97	236-238	62.04
7e			C25H16ClN5OS	469.95	268-270	54.76
7f			C26H19N5O2S	465.53	271-273	56.33
7g			C26H18BrN5OS	528.42	289-291	47.89



Compounds	R1	R2	Molecular formula	Molecular wt	Melting Point °C	% Yield
7h			C17H14N4S	306.38	230-232	45.04
7i			C17H14N4OS	322.38	138 – 140	41.02
7j			C20H14N4S	342.42	232-234	54.43

The structure of target compounds were characterized by IR, ^{1}H NMR and Mass spectra. The ^{1}H NMR spectrum of compound 7b showed a multiplet signals in the region of 6.4-7.9 δ ppm corresponding to the 14H aromatic proton, a singlet signal at 3.9 δ ppm for NH proton, a singlet signal at 3.48 δ ppm for CH_3 groups, (3H). The mass spectrum revealed a molecular ion peak at m/z = 484.09 (M+1) corresponding to a molecular formula C26H18ClN5OS. The IR spectrum showed absorption bands at 1730 cm^{-1} due to carbonyl groups, 3329 due to NH group, 719 for CH, b, aromatic, 3010 due to CH, s, aromatic, 2200 for CN, 1606 due to C=C aromatic. The detailed results of spectral analysis were described in experimental part. The physical data of compounds**7a**-**7j** were given in table 1.

Molecular Docking

COX2 enzyme (pdb code: 1CX2) in complex with co-crystallized ligand SC 558 was used for molecular docking study. For each docking experiment, the lowest energy docked structure was selected from 10 runs. The docking results were revealed in Table 2. SC 558 involved in hydrogen bond interaction with ARG 120 and TYR 115 with binding energy -7.49 kcal/mol (Fig 1). Compound **7a** was found to interact with ARG 120 and PRO 84, with lowest binding energy -9.32 kcal/mol (Fig 2). **7e** was found to have minimum binding energy -8.34 kcal/mol and interact with TYR 115 and SER 119 (Fig 3). Compounds **7h** and **7i** involved in hydrogen bond interaction with ARG 120 and TYR 115. Although **7b** and **7c** show minimum binding energy but did not form hydrogen bond with any amino acid residue on target protein. All compounds show improved binding energies in comparison with SC 558.

Table 2: Docking results showing Binding energy, inhibition constant and amino acids involved in hydrogen bonding for compounds 7a-7j

Compounds	Binding Energy kcal/mol	Inhibition constant	No of bonds	Amino acids involved in hydrogen bonding
7a	-9.32	148.52 nM	2	ARG 120, PRO 84
7b	-9.59	93.35 nM	-	-
7c	-9.11	209.1 nM	-	-
7d	-8.14	1.09 µM	1	ARG 120
7e	-8.34	770.86 nM	2	TYR 115, SER 119
7f	-7.26	4.78 µM	1	ARG 120
7g	-9.59	92.91 nM	1	LYS 83
7h	-7.79	1.94 µM	2	ARG 120, TYR 115
7i	-7.09	6.37 µM	2	ARG 120, TYR 115
7j	-7.87	1.71 µM	1	ARG 120
SC-558	-7.49	3.21 µM	2	ARG 120, TYR 115

Anti-inflammatory activity

Title compounds were screened for their *in vivo* anti-inflammatory activity in carrageenan induced rat paw edema model. Percent inhibition of standard drug diclofenac sodium and tested compounds were calculated in comparison with vehicle control (Table 3). Compounds **7e, 7h, 7c** and **7j** possess significant anti-inflammatory activity at second phase but less than diclofenac sodium. Compounds **7a, 7b, 7d, 7f, 7g,** and **7i** shows moderate anti-inflammatory activity. These results suggest that Cl group at para position of phenyl ring is essential for activity. The results showed that inhibition of paw edema occur at time 4-6 h duration after carrageenan injection. This indicate that compounds might be showing its anti-inflammatory action by inhibiting prostaglandin synthesis.

Table 3: Effect of 4-amino-5-(4-oxo-3-aryl-3,4-dihydroquinazolin-2-yl)-2 (arylamino)thiophene-3-carbonitrile on Carrageenan induced paw edema

Compound	Edema volume (ml) mean ± SEM (% inhibition)					
	1 h	2 h	3 h	4h	5h	6h
Control	1.125 ± 0.010	1.24 ± 0.01	1.48 ± 0.018	1.57 ± 0.031	1.38 ± 0.016	1.20 ± 0.015
DS	0.94± 0.012*(15.85)	0.77 ± 0.021** (37.76)	0.68 ± 0.023**(53.64)	0.59± 0.009**(62.15)	0.54 ± 0.013**(60.60)	0.53 ± 0.012**(55.58)
7a	1.10 ± 0.006 (2.07)	1.12 ± 0.008(9.13)	1.15 ± 0.012(22.1)	1.10 ± 0.013* (30.12)	1.06 ± 0.009* (23.01)	0.96 ± 0.027* (17.7)
7b	1.06 ± 0.014 (5.18)	1.11 ± 0.010 (10.08)	1.12 ± 0.006 (24.57)	1.09± 0.017*(30.76)	1.08 ± 0.007 (21.92)	1.05 ± 0.008 (10.33)
7c	1.05 ± 0.012 (6.07)	1.06 ± 0.020 (14.38)	1.09 ± 0.016* (26.37)	1.05 ± 0.016* (33.29)	1.02 ± 0.009* (26.02)	0.98 ± 0.007* (16.57)
7d	1.07 ± 0.004 (4.29)	1.08 ± 0.011 (12.36)	1.10 ± 0.004 (25.7)	1.07± 0.014* (31.92)	1.05± 0.010* (23.49)	0.99 ± 0.007 (15.72)
7e	1.03 ±0.016 (8.0)	1.05 ± 0.013* (15.05)	1.08 ± 0.011* (27.10)	0.86 ± 0.032**(45.34)	0.85 ± 0.007* (38.07)	0.82 ± 0.015* (29.6)
7f	1.10 ± 0.014 (1.48)	1.12 ± 0.012 (9.27)	1.13 ± 0.005* (23.9)	1.06± 0.018*(32.55)	0.99 ± 0.036*(27.83)	0.97 ± 0.036 (17.28)
7g	1.08 ± 0.009 (3.40)	1.10 ± 0.004 (10.61)	1.11 ± 0.009* (24.91)	1.08 ± 0.010* (31.5)	1.01 ± 0.012*(26.5)	0.98 ± 0.009 (16.43)
7h	1.02 ± 0.024 (8.59)	1.04 ± 0.003 (16.12)	1.07 ± 0.010*(27.83)	0.83± 0.021** (47.25)	0.82 ± 0.033* (40.6)	0.79 ± 0.013* (32.43)
7i	1.09 ± 0.003 (2.37)	1.10 ± 0.017 (10.61)	1.12 ± 0.020 (24.24)	1.11 ± 0.010* (29.38)	1.02 ± 0.008* (25.66)	0.97 ± 0.018* (17.28)
7j	1.09 ± 0.011 (3.11)	1.09 ± 0.014* (11.42)	1.10 ± 0.010 (25.58)	1.04 ± 0.037* (33.82)	0.96 ± 0.011* (30.48)	0.93 ± 0.009* (20.39)

Each value is the mean ± SEM for six rats. *P < 0.05, **P < 0.01, Statistical analysis by one way ANOVA followed by Dunnett's test by using graph pad prism 7.
Control: 0.5 % sodium CMC
DS: Standard Diclofenac Sodium

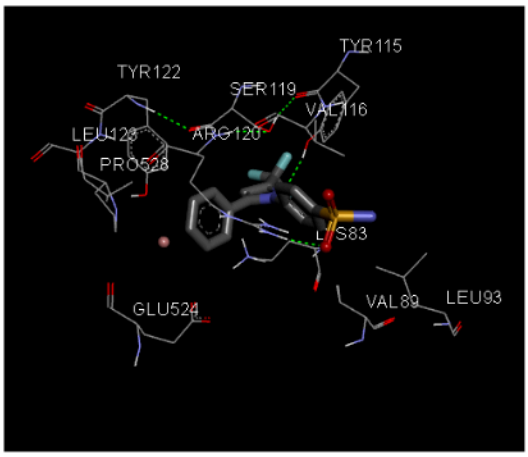


Fig 1: SC558 binding with receptor 1CX2

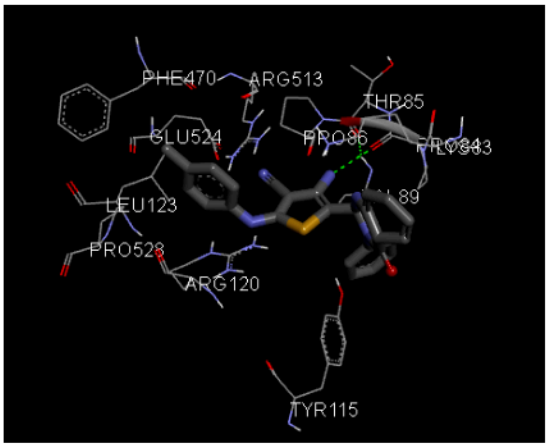


Fig 2: 7a binding with receptor 1CX2

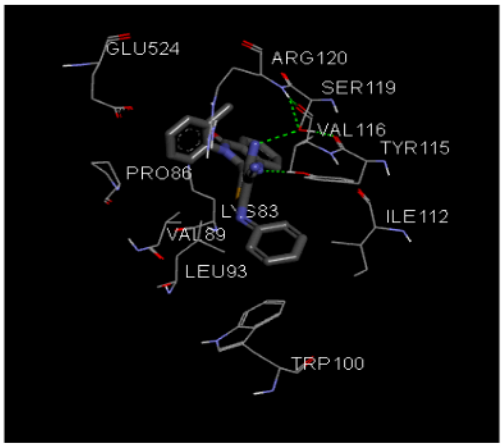


Fig 3: 7e binding with receptor 1CX2

CONCLUSION

In an attempt to discover potential anti-inflammatory agent a series of novel tetrasubstituted thiophene derivatives were synthesized. The compounds **7e** and **7h** exhibited comparable anti-inflammatory activity as compared to standard drug diclofenac sodium. Remaining all compounds possess mild anti-inflammatory activity. All the final compounds were docked into binding pocket of COX2 enzyme. Docking results of some compounds revealed lowest binding energies and involved in hydrogen bond interaction with binding site. In conclusion, tetrasubstitued thiophenes can be explored more for further development of novel anti-inflammatory drugs.

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REFERENCES

1. Zarghi A, Arfaei S. Selective COX-2 Inhibitors: A Review of Their Structure-Activity Relationships. Iranian Journal of Pharmaceutical Research. 2011; Volume 10, Issue 4, 655-683.
2. Karna J, Laxminarayana H, Krishna E, Merugu GR. Synthesis, Characterization, And Molecular Docking For Anti-Inflammatory Activity Of 4-(4-Chlorophenyl)-6-Aryloxypyrimidines. Indian Journal Of Heterocyclic Chemistry. 2017; Volume 27, Issue 2, 189-193.
3. Shanmuganathan T, Parthasarathy K, Venugopal M, Arun Y, Dhatchanamoorthy N, Prince AM. Synthesis, in vitro anti-inflammatory activity and molecular docking studies of novel 4,5-diarylthiophene-2-carboxamide derivatives. Journal of Chemical Sciences. 2017; Volume 129, Issue 1, 117-130.
4. Nikalje AP, Hirani N, Nawle R. Synthesis, in-vitro, in-vivo evaluation and molecular docking of 2-(3-(2-(1, 3-dioxoisoindolin-2-yl)acetamido)-4-oxo-2-substituted thiazolidin-5-yl) acetic acid derivatives as anti-inflammatory agents, African Journal of Pharmacy & Pharmacology. 2015; Volume 9, Issue 7, 209-222.
5. Radwan MA, Fakhr MI, Seham EB, Omar ME, El-Salam A. Synthesis and pharmacological evaluation of 2- substituted benzo[b]thiophenes as anti-inflammatory and analgesic agents. European Journal of Medicinal Chemistry. 2009; Volume 44 1718-1725.
6. Kolomoets, Voskoboynik O, Antypenko O, Berest G, Nosulenko I. Design, Synthesis and Anti-inflammatory Activity of Derivatives 10-R-3-Aryl-6,7-dihydro-2H-[1,2,4] triazino[2,3-c]quinazolin-2-ones of Spiro-fused Cyclic Frameworks. Acta Chimica Slovenica. 2017; Volume 64, 902-910.
7. Srivastava S, Das B, Prasad. R. Antimicrobial and anti-inflammatory effect of some novel tetra substituted Thiophenes. Der Pharmacia Lettre, 2012; Volume 4, 1214-1220.
8. Mishra R, Jha KK, Kumar S, Tomer I. Synthesis, properties and biological activity of thiophene: A review. Der Pharma Chemica. 2011; Volume 3, Issue 4, 38-54
9. Parai MK, Panda G, Chaturvedi V, Manjuand YK, Sinha S. Thiophene containing triarylmethanes as antitubercular agents. Bioorganic & Medicinal Chemistry Letters. 2008; Volume 18, 289-292.
10. Romagnoli R, Baraldi PG, Lopez OC, Tolomeo M, Cristina AD. Synthesis of novel antimitotic agents based on 2-amino-3-aroyl-5-(hetero)arylethynyl thiophene derivatives. Bioorganic & Medicinal Chemistry Letters. 2011; Volume 21, 2746-2751.
11. Patrizia D, Carbone A, Barraja P, Montalbano A, Martorana A, Dattolo G. Synthesis and antitumor properties of 2,5-bis(30-indolyl) thiophenes: Analogues of marine alkaloid nortopsentin. Bioorganic & Medicinal Chemistry Letters. 2007; Volume 7, 2342-2346.
12. Valderrama J, Fournet A, Valderrama BC, Bastias AS. Synthesis and in vitro antiprotozoal activity of thiophene ring-containing quinones. Chemical & Pharmaceutical Bulletin. 1999; Volume 47, Issue 9, 1221-1226.
13. Datta S, Kavitha PN, Singh A. Synthesis, Characterization and Docking Studies of Some New Thiophene Derivatives and Their In-Vitro Anti-Microbial Screening. International Journal of Pharmacology & Pharmaceutical Sciences. 2015; Volume 3, 10-17
14. El-Haggar R, Abdel-Rasheed OA, Nasr T, Ali HI. Synthesis, evaluation and molecular docking studies for the anti-inflammatory activity of novel 8-substituted 7-benzoyloxy-4-methyl-6-nitrocoumarin derivatives. African Journal of Pharmacy & Pharmacology. 2014; Volume 8, 1213-1227.
15. Giri RS, Thaker HM, Giordano T, Williams J, Rogers D, Sudarsanam V, Vasu KK. Design, synthesis and characterization of novel 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazoline-4-one derivatives as inhibitors of NF-kB and AP-1 mediated transcription activation and as potential anti-inflammatory agents. European Journal of Medicinal Chemistry. 2009; Volume 44, 2184-2189.
16. Giri RS, Thaker HM, Giordano T, Williams J, Rogers D, Sudarsanam V, Vasu KK. Design, synthesis and evaluation of novel 2-thiophen-5-yl-3H-quinazolin-4-one analogues as inhibitors of transcription factors NF-kB and AP-1 mediated transcriptional activation: Their possible utilization as anti-inflammatory and anti-cancer agents. Bioorganic & Medicinal Chemistry. 2010; Volume 18, 2796-2808.
17. Wang Y, Huang J, Chai Y, Liu Q, Liang Y, Dong D. Efficient One-Pot Synthesis of Highly Substituted Thiophene Library from 1, 3- Dicarbonyl Compounds. Journal of Combinatorial Chemistry. 2008; Volume 10, 511–516.
18. Sommen G, Comel A, Kirsch G. Preparation of thieno [2,3-b] pyrroles starting from ketene-N, S-acetals. Tetrahedron. 2003; Volume 59, 1557–1564.
19. Winter CA, Risley EA, Nuss GW. Carrageenan-induced edema in hind paw of the rat as an assay for anti-inflammatory drugs. Proceedings of the Society for Experimental Biology & Medicine. 1962; Volume 111, 544–547.

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