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SHORT COMMUNICATION

Synthesis and pharmacokinetic study of new thiazole derivatives containing pyrazole moiety

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ABSTRACT

For developed new eco-friendly synthetic route for the synthesis of organic compounds, here in, we have synthesized new series of thiazole derivatives 7(a-h) under microwave irradiation method using less amount of methanol as solvent and less hazardous K_2CO_3 as catalyst. Then after for the pharmacokinetic study, we can calculate Lipinski rules of five data using swiss ADME software, molecule 7f was fitted in 'rules of five' (Ro5) other compounds are showed violence in log P(o/w). The structures of all synthesized compounds are well characterized by Mass, ^{1}H NMR, ^{13}C NMR.

***Keywords*:** Thiazole, Pyrazole, Microwave irradiation, Pharmacokinetic, eco-friendly

1. INTRODUCTION

Thiazole ring systems are important class of heterocyclic compounds not only for their synthetic aspects but also known for their wide range of therapeutic interest in medicinal chemistry. It is five member heterocyclic molecule having both nitrogen and sulphur atom.

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Many of the synthetic therapeutic drugs are known to havening thiazole motif such as antimicrobial acinitrazole and sulfathiazole,[1] antibiotic penicillin,[2] antineoplastic agent bleomycin and tiazofurin,[3] antidepressant pramipexole,[4] anti HIV drugs ritonavir,[5] antiasthamatic drug cinalukast[6] and antiulcer agent nizatidine[7] containing thiazole ring system. It also presents in natural (Vitamin B_1-Thiamine)[8] and other medicinally important compounds. Reduced thiazoles serve in the study of polypeptides and proteins and occur as structural units in compounds of biological importance.[9]

On the other hand five member pyrazole key structure also possess wide range of biological activity, in the literature survey reveals such as analgesic, anti-infammatory, antipyretic,[10] anti-depressant,[11] cytotoxic,[12] anti-oxidant,[13] antimicrobial[14-15] etc. among them analgesic and anti-inflammatory are more important. Many of the drugs known to having pyrazole derivatives and found to their application as NSAIDs such as Antipyrine, Dipyrone, Aminopyrine, Phenylbutazone etc.[16] Thiazole was first described by Hantzsch and Weber in 1887,[17] then after many of researcher have been synthesised and evaluate their biological importance. Since the combination of both pharmacophores on the same scaffold is a well-recognized manner to the synthesis of more potent biological active compounds. There for we decided to combine pyrazole moiety and thiazole ring in the same molecule and synthesizing new series of bioactive heterocycles. Now a day, researcher must give the attestation to use less hazardous solvent and metal catalyst, and developed economically viable method for the synthesis of particular compoundas.[18]

Chemistry discussion

For green chemistry approach, we have synthesised new series of compounds **7(a-h)** by microwave assisted method of organic synthesis using less hazardous Inorganic potassium salt K_2CO_3 as catalyst and less amount of methanol as solvent for carried out the synthesis. This method takes less time for complete conversion in desire yields than ordinary conventional method. First of all we have synthesised chalcone intermediate from 2- acetyle furan and 4-isopropyl benzaldehyde as reported method.[19] then synthesised chalcone on reaction with thiosemicarbeazide in presence of catalytic amount of KOH gives pyrazole key intermediate. Our target molecules 7(a-h) were prepared by green microwave irradiation method of synthesis, from that purpose we used less solvent and less hazardous K_2CO_3 catalyst. All the compounds are well characterised by Mass, ^{1}H NMR, ^{13}C NMR. The pharmacokinetic study of all the compounds were done by using swiss ADME software, and calculate Lipnski's rule of five (Ro5) like water solubility (logS), polar surface area (PSA) etc. In the present study, here compound 7f was fitted in Lipinski's rule of five with molecular weight less than 500 g/mol (Table 3), HBA less than 10, HBD less than 5 & log P values less than 5 and The polar surface area ($\leq$ 140 °A^2). All other compounds obey all the parameter in Ro5 but violence in log P value, it is greater than 5. Here the lipophilicity was not less 5 according to Ro5 rule so not orally absorbed.

2. MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV. IR spectra were recorded in Shimadzu FT-IR-8400

instrument using KBr method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in $CDCl_3$/DMSO solution on a Bruker Ac 400 MHz spectrometer. All the reactions were carried out in Q-pro-M microwave synthesizer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

3. EXPERIMENTAL PROCEDURE

General procedure for the synthesis of 1-(furan-2-yl)-3-(4-isopropylphenyl)prop-2-en-1-one: (Scheme 1)

Take an Equimolar mixture of 2 acetyl furan (0.01 mole) and isopropyl benzaldehyde(0.01 mole) in 5 ml methanol, add 40% KOH solution drop wise until solution become basic. Reflux the reaction mixture for 10 hrs. Reaction was monitored by using TLC. After completion of reaction, reaction mixture poured on to crushed ice, acidify with HCl and isolate product filtered and used in next step without any purification.[19]

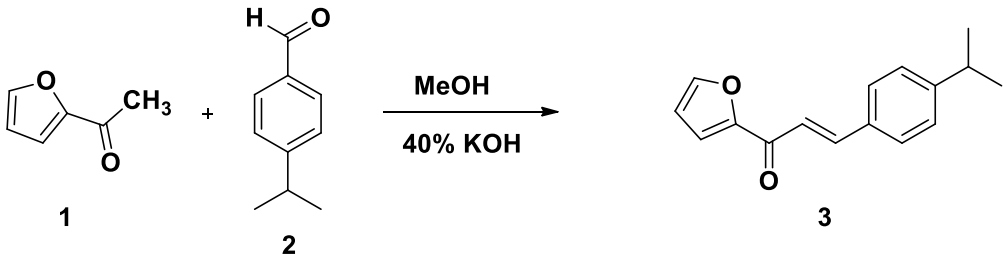
General procedure for the synthesis of 3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazole-1-carbothioamide: (Scheme 2)

A solution of 1-(furan-2-yl)-3-(4-isopropylphenyl)prop-2-en-1-one (3) (0.01 mol) and thiosemicarbazide (4) (0.02 mol) in absolute ethanol (25 ml) and add catalytic amount of KOH reflux the reaction mixture about 10 hrs. and left overnight. The separated solid was collected and washed with water and crystallized from acetonitrile.[20]

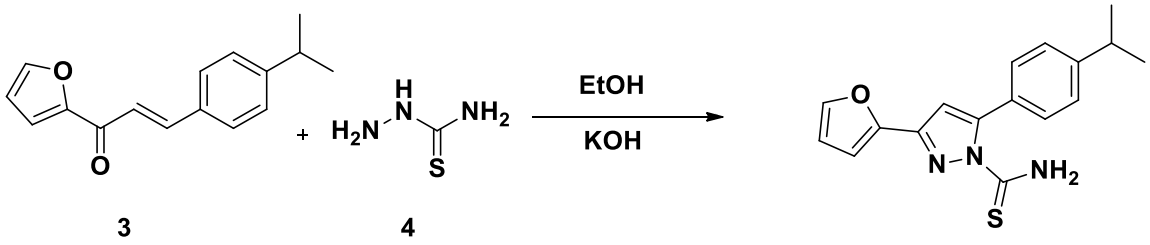
General procedure for the synthesis of 2-(3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazol-1-yl)-4-(substituted phenyl)-2,5-dihydrothiazole: (Scheme-3)

3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazole-1-carbothioamide (0.01 mol), 2-bromo 1-substituted phenylethanone (0.01 mol), catalytic amount of K_2CO_3 and 5 ml methanol charged in round bottom flask. The reaction mixture was irradiated in microwave about 25-28 minutes. Reaction was monitored by TLC using ethyl acetate and hexane (3:7). At the time of completion of reaction the reaction mass was poured in ice cold water and the separated solid was filtered, dried and crystallized from ethanol.

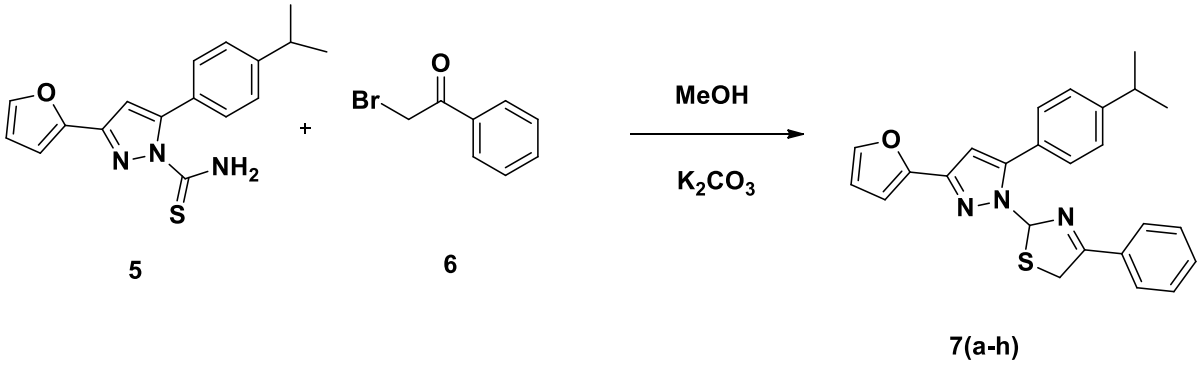
3. 1. Reaction Scheme



Scheme 1



Scheme 2



Scheme 3

Table 1. Optimization of yield for the microwave assisted as well as conventional method of synthesis of 7a, using different solvents.

Entry	Solvent	Time (MWI)	% yield
1	Hexane	40	10
2	Diethyl ether	40	10
3	Dichloromethane	35	60
4	Chloroform	35	70
5	Ethylacetate	30	70
6	Ethanol	30	80
7	Methanol	25	88

Table 2. Synthesis of substituted thiazole derivatives 7(a-h) by Microwave assisted method of synthesis.

Entry	Compound	Substitution	Time(MWI)	% yield	MP (ºC)
1	**7a**	-H	25	88	184
2	**7b**	$-CH_3$	25	84	186
3	**7c**	-Br	28	80	190
4	**7d**	-F	28	82	192
5	**7e**	-Cl	28	82	196
6	**7f**	$-NO_2$	25	80	210
7	**7g**	-CN	25	80	202
8	**7h**	$-OCH_3$	25	82	198

Table 3. Kinetic study of synthesised 7(a-h)

Entry	4a	4b	4c	4d	4e	4f	4g	4h
M.W [a]	413.53	427.56	492.43	431.53	447.98	458.53	438.54	443.56
Log Po/w[b]	5.30	5.63	5.91	5.60	5.83	4.54	5.07	5.29
HBA[c]	3	3	3	4	3	5	4	4
HBD[d]	0	0	0	0	0	0	0	0
PSA[e] **($^oA^2$)**	68.62	68.62	68.62	68.62	68.62	114.44	92.41	77.85
Log S [f]	-6.37	-6.66	-7.27	-6.52	-6.96	-6.42	-6.31	-6.43
Rot [g]	5	5	5	5	5	6	5	6
Log k_n [h] **cm/s**	-4.60	-4.43	-4.59	-4.64	-4.36	-4.99	-4.95	-4.80

a = Molecular weight; b= partition co efficient octanol water system; **c** = Hydrogen bond acceptor; **d** = Hydrogen bond donor; **e** = Polar surface area; f = solubility in water; **g** = Rotatable bonds; h = penetration in skin

3. 2. Spectral Data

2-(3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazol-1-yl)-4-phenyl-2,5-dihydrothiazole (7a)

Mp: 184 ºC , Chemical Formula: $C_{25}H_{23}N_3OS$; MS (m/z): 413, Elemental Analysis: C, 72.61; H, 5.61; N, 10.16; O, 3.87; S, 7.75, ^{1}H NMR: δ 1.13-1.18 (6H, d), 2.91 (1H, sept), 4.22-4.30 (2H, d), 6.44 (1H, dd), 6.65 (1H, s), 6.78 (1H, dd), 7.11 (1H, s), 7.1 (2H, dd), 7.41-7.51 (3H, dd) , 7.44 (1H, t), 7.66 (2H, dd), 8.25 (2H, dd). ^{13}C NMR (101 MHz, $CDCl_3$), δ 107.14, 126.2, 127.2, 127.2, 142.3, 128.3, 128.3, 150.5, 128.9, 144.6, 153.8, 153.8, 150.9, 128.7, 128.7, 33.9, 23.8, 23.8, 36.8, 130.6, 111.8, 126.8, 126.8,112

2-(3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazol-1-yl)-4-(p-tolyl)-2,5-dihydrothiazole (7b)

MP 186 ºC; Chemical Formula: $C_{26}H_{25}N_3OS$; MS (m/z) 427.17; Elemental Analysis: C, 73.04; H, 5.89; N, 9.83; O, 3.74; S, 7.50; ^{1}H NMR: δ 1.14-1.19 (6H, d), 2.28 (3H, s), 2.98 (1H, sept), 4.00 (1H, d), 4.20 (1H, d), 6.45 (1H, dd), 6.77 (1H, s), 6.78 (1H, dd), 7.11 (1H, s), 7.15-7.24 (4H, dd), 7.58-7.69 (4H, dd), 7.75 (1H, dd), ^{13}C NMR (101 MHz, $CDCl_3$), δ 21.2, 150.9, 36.8, 111.8, 128.3, 128.3, 130.6, 126.2, 129.32, 129.32, 139.7, 142.3, 150.5, 125.1, 125.1, 23.8, 107.14, 33.9, 126.8, 126.8, 153.8, 153.8, 112, 144.6, 23.8

4-(4-bromophenyl)-2-(3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazol-1-yl)-2,5-dihydrothiazole (7c)

MP 190 ºC; Chemical Formula: $C_{25}H_{22}BrN_3OS$; MS (m/z) 491.07; Elemental Analysis: C, 60.98; H, 4.50; Br, 16.23; N, 8.53; O, 3.25; S, 6.51; ^{1}H NMR: δ 1.10-1.13 (6H, d), 2.98 (1H, sept), 3.99 (1H, d), 4.15 (1H, d), 6.44 (1H, dd), 6.74 (1H, s), 6.78 (1H, dd), 7.18 (1H, s), 7.12-7.23 (4H, dd), 7.66 (2H, ddd), 7.78 (1H, dd), 7.94 (2H, ddd). ^{13}C NMR (101 MHz, $CDCl_3$), δ 150.975, 150.5, 144.6, 142.3, 131.2, 131.2, 130.6, 128.86, 128.8, 128.31, 128.31, 126.81, 126.8, 126.2, 124.0, 112, 111.8, 107.14, 36.82, 33.93, 23.85, 23.8,

4-(4-fluorophenyl)-2-(3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazol-1-yl)-2,5-dihydrothiazole (7d)

MP 192 ºC; Chemical Formula: $C_{25}H_{22}FN_3OS$; MS (m/z) 431.15; Elemental Analysis: C, 69.58; H, 5.14; F, 4.40; N, 9.74; O, 3.71; S, 7.43; ^{1}H NMR: δ 1.12-1.19 (6H, d), 2.87 (1H, sept), 3.99 (1H, d), 4.18 (1H, d), 6.44 (1H, dd), 6.74 (1H, s), 6.78 (1H, d), 7.18 (1H, s), 7.15-7.23 (4H, dd), 7.66 (2H, ddd), 7.77 (1H, dd), 7.94 (2H, ddd); ^{13}C NMR (101 MHz, $CDCl_3$), δ 153.83, 153.8, 150.9, 150.5, 144.6, 142.3, 135.6, 130.65, 128.7, 128.71, 128.6, 128.64, 128.3, 128.31, 126.8, 126.8, 126.2, 112, 111.8, 107.14, 36.82, 33.93, 23.85, 23.85,

4-(4-chlorophenyl)-2-(3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazol-1-yl)-2,5-dihydrothiazole (7e)

MP 196 ºC; Chemical Formula: $C_{25}H_{22}ClN_3OS$; MS (m/z) 447.12 ; Elemental Analysis: C, 67.03; H, 4.95; Cl, 7.91; N, 9.38; O, 3.57; S, 7.16; ^{1}H NMR: δ 1.16-1.20 (6H, d), 2.98 (1H, sept), 4.11 (1H, d), 4.10 (1H, d), 6.49 (1H, dd), 6.80 (1H, s), 6.84 (1H, dd), 7.18 (1H, s), 7.24 (2H, ddd), 7.53 (2H, ddd), 7.61-7.69 (4H, dd), 7.75 (1H, dd); ^{13}C NMR (101 MHz, $CDCl_3$), δ 163.35, 153.83, 153.8, 150.9, 150.5, 144.6, 142.35, 130.65, 128.31, 128.3, 127.7, 127.7, 126.81, 126.8, 126.2, 115.9, 115.9, 112, 111.8, 107.14, 36.82, 33.93, 23.8, 23.85,

2-(3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazol-1-yl)-4-(4-nitrophenyl)-2,5-dihydrothiazole (7f)
MP 210 ºC; Chemical Formula: $C_{25}H_{22}N_4O_3S$; MS (m/z) 458.14; Elemental Analysis: C, 65.48; H, 4.84; N, 12.22; O, 10.47; S, 6.99; ^{1}H NMR: δ 1.11-1.14 (6H, d), 3.0 (1H, sept), 3.94 (1H, d), 4.13 (1H, d), 6.44 (1H, dd), 6.74 (1H, s), 6.78 (1H, dd), 7.19 (1H, s), 7.18 (2H, ddd), 7.66 (2H, ddd), 7.74-7.81 (3H, dd), 7.96 (2H, ddd); ^{13}C NMR (101 MHz, $CDCl_3$), δ 153.83, 153.8, 150.9, 150.55, 144.6, 142.35, 140.47, 131.2, 131.2, 130.65, 128.31, 128.3, 126.8, 126.8, 126.2, 117.29, 117.29, 112, 111.8, 107.14, 36.82, 33.93, 23.85, 23.8,

4-(2-(3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazol-1-yl)-2,5-dihydrothiazol-4-yl)benzonitrile (7g)
MP 202 ºC; Chemical Formula: $C_{26}H_{22}N_4OS$; MS (m/z) 438.15; Elemental Analysis: C, 71.21; H, 5.06; N, 12.78; O, 3.65; S, 7.31; ^{1}H NMR: δ 1.14-1.19 (6H, d), 2.96 (1H, sept), 3.92 (1H, d), 4.13 (1H, d), 6.48 (1H, dd), 6.80 (1H, s), 6.88 (1H, dd), 7.13 (1H, s), 7.19 (2H, ddd), 7.78 (2H, ddd), 7.78-7.97 (3H, dd), 7.96 (2H, ddd); ^{13}C NMR (101 MHz, $CDCl_3$), δ 153.83, 153.8, 150.9, 150.55, 144.6, 142.35, 140.47, 142.35, 132.2, 131.2, 130.65, 128.31, 128.3, 126.8, 126.8, 126.2, 125.19, 118.29, 117.29, 112, 111.8, 107.14, 36.82, 33.93, 23.85, 23.8,

2-(3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazol-1-yl)-4-(4-methoxyphenyl)-2,5-dihydrothiazole(7h)
MP 198 ºC; Chemical Formula: $C_{26}H_{25}N_3O_2S$; MS (m/z): 443.17; Elemental Analysis: C, 70.40; H, 5.68; N, 9.47; O, 7.21; S, 7.23; ^{1}H NMR: δ 1.10-1.18 (6H, d), 2.83 (1H, sept), 3.80 (3H, s), 3.88 (1H, d), 4.24 (1H, d), 6.44 (1H, dd), 6.59 (1H, s), 6.78 (1H, dd), 7.13 (1H, s), 7.10-7.28 (4H, dd), 7.56-7.69 (4H, dd), 7.75 (1H, dd); ^{13}C NMR (101 MHz, $CDCl_3$), δ 160.41, 153.83, 153.8, 150.9, 150.55, 144.6, 142.35, 130.65, 128.6, 128.69, 128.31, 128.3, 126.81, 126.8, 126.2, 114.07, 114.07, 112, 111.8, 107.14, 55.46, 36.8, 33.93, 23.8, 23.8

4. CONCLUSIONS

We have prepared a library of novel 2-(3-(furan-2-yl)-5-(4-isopropylphenyl)-1H-pyrazol-1-yl)-4-(substituted phenyl)-2,5-dihydrothiazole (7a-7h) using inorganic base and less amount methanol as solvent by microwave irradiation method. We obtained good yields and highly pure compounds within less reaction time. We also studied pharmacokinetic parameter of all synthesised compound, from which molecule 7f possess zero violence in limpkin's rule of five.

So, could possess drug likes properties.

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