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Der Chemica Sinica, 2015, 6(12):12-18

Der Chemica Sinica
Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Convenient synthesis of thiazole derivatives grouping with pyrazole ring under the microwave

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ABSTRACT

Here in, we have synthesised the series of pyrazole bearing thiazole derivatives and optimized the solvent, reaction time and % yield in microwave assisted as well as conventional method. The reaction of 4-substituted phenacylbromide with thioamide using piperidin as a catalyst and methanol as a solvent yielded series of substituted thiazole ***(7a-h).*** *After obtaining experimental data concerning the yield and the time taken for the synthesis by both the methods, conventional and microwave assisted method, it was proved that the microwave assisted method is convenient for synthesis of new series of 2-(2-((3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene) hydrazinyl) -4-sustituted phenyl-2, 5-dihydrothiazole [7a-h]. The structures of all synthesized compounds are well characterized by Mass, FT-IR,* ^{1} *H NMR,* ^{13}*C NMR.*

Key words: Pyrazole aldehyde, Microwave, Methanol, Piperidin.

INTRODUCTION

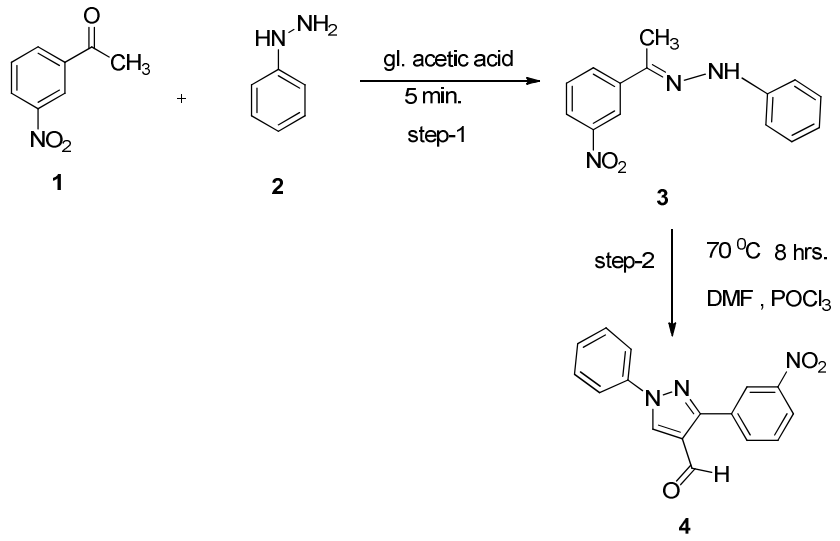
Thiazole ring system in the frequent biologically active molecules has been notorious which plays an important role in animal and plant kingdom. Different substituted thiazole bearing compounds possess different kinds of activities [1-3], such as anti- fungal [4], anti-bacterial [5], anthelmintic, antihypertensive, anti-inflammatory [6], anti-HIV [7], MAO inhibitors [8-9] etc. Some of the active drugs available in the market bearing the thiazole moiety like ritonavir [10], fanetizole and meloxicam [11-12], imidaclopride and well known antibiotic penicillin. Some of the chiral thiazol based motif act as histone acetyltrasferase inhibitors [13]. Thus the thiazole nucleus has attracted much interest in the development of pharmacologically active compounds.

On the other hand, Many of the pyrazolone compounds have been reported for potential therapeutic agents, such as anti-bacterial [14] anti-cancer [15], also act as histon acetyltransferase inhibitor [16] and non-steroidal anti-inflammatory agent [17-21], that occurs in the many drugs including the marketed like selective COX-2 drug(celecoxib), that have been shown to be well sanction with reduced GIT side effects. Some of the prior urbanized pyrazolone based drugs like antipyrine and amidopyine have been excluded as they are found to have serious side effects like bone marrow depression, agranulocytosis and blood dyscriasis.

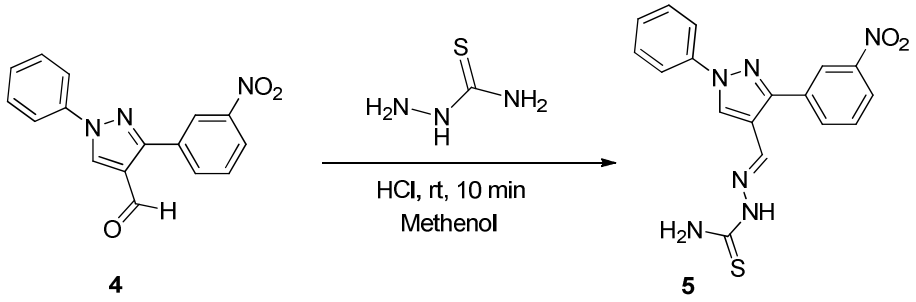
Since the combination of both pharmacophores on the same scaffold is a well-recognized attitude to the synthesis of more potent drugs. There for we decided to combine pyrazole moiety and thiazole ring in the same molecule and synthesizing new series of bioactive heterocycles.

MATERIALS AND METHODS

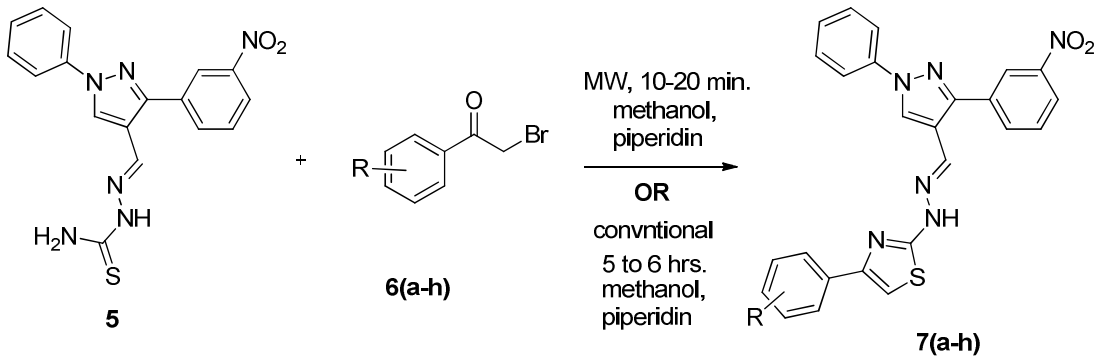
Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV. IR spectra were recorded in Shimadzu FT-IR-8400 instrument using KBr method. Mass spectra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



Scheme-1



Scheme -2



Scheme-3

Preparation of pyrazole aldehyde:

Step – 1: Preparation of 1-(1-(3-nitrophenyl)ethylidene)-2-phenylhydrazine:

3-Nitro Acetophenone (0.1 mol) was dissolved in 50 ml of ethanol into 250 ml R.B.F. Phenyl hydrazine (0.1 mol) was added to above flask along with 3-4 drops of glacial acetic acid. The reaction mixture was stirred for 5 min. at room temperature. The progress and the completion of reaction were monitored by TLC using ethyl acetate: hexane (6:4) as a mobile phase. After the completion of the reaction, the reaction mixture was kept to room temperature for 1 h and the crystalline product was filtered, washed with ethanol and dried at room temperature to give substituted

acetone phenyl hydrazone in good yield which was pure enough to use as such for the next step. The Physical constants of newly synthesized compounds were compared with the standard data.[22]

Step – 2: Preparation of 3-(3-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde:
Dimethylformamide (0.32 mol) was transferred into 25 ml flat bottom flak. Phosphorous oxychloride (0.032 mol) was added under controlled rate under stirring so that temperature does not rise above 5°C. After complete addition, the mixture was raised to temperature and allows it to stir for 10-15 min. freshly prepared acetophenone hydrazone 0.03 mole was added to above mixture and the content was heated on water bath at 70^0C for 8 hours. The progress and the completion of reaction were monitored by TLC using toluene: ethyl acetate (6: 4) as a mobile phase. After the completion of the reaction, mixture was cooled to room temperature and the content of the flask was poured on crushed ice to isolate the product. The separated product was filtered and washed with 1L cold water to remove complete acidity. It was further dried at 65°C and recrystallized from the mixture of DMF-Methanol to give crystalline pyrazole aldehyde in good yield. The Physical constants of newly synthesized compounds were compared with the standard data.[22]

Preparation of 2-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4 yl)methylene) hydrazinecarbothioamide.
3-(3-Nitrophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde(0.01mole), thiosemicarbazide (0.01mole) and one drops of hydrochloric acid were stirred for 10 min. The progress of the reaction was monitored by TLC. On the completion of the reaction, reaction mixture was poured into crushed ice and seperted product was filtered, dried and recrystallized from ethanol. [23]

Preparation of 2-(2-((3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) hydrazinyl) -4-sustitutedphenyl-2,5-dihydrothiazole.
2-(3-(3-Nitrophenyl)-1-phenyl-1H-pyrazol-4 yl)methylene) hydrazinecarbothioamide, 2-bromo 1-substituted phenylethanone(0.01mol), catalytic amount of piperidin and 10 ml methanol charged in round bottom flask. The reaction mixture was hated about 5-6 hours in conventional method and in microwave, irradiated about 10-20 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 [23].

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

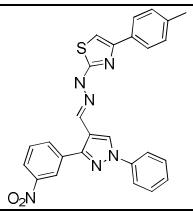
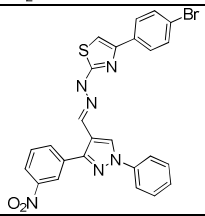
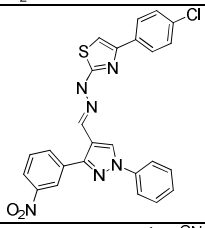
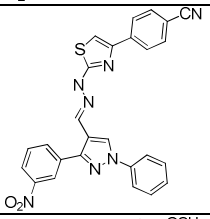
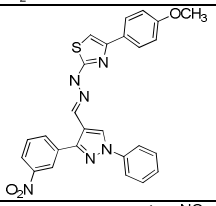
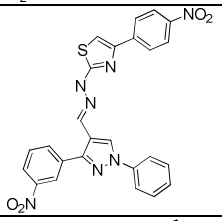
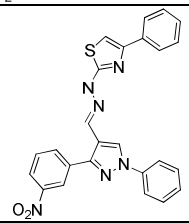
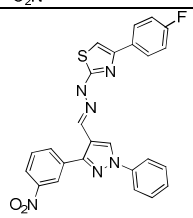
Entry as	Solvent	Time[a] (min) MWI	Yield[a] % MWI	Time[b] (hrs.) conventional	Yield[b] % conventional
7a	Methanol	15	85	6	60
7b	Methanol	20	80	6	55
7c	Methanol	15	85	6	58
7a	Dichloromethane	30	70	9	40
7b	Dichloromethane	35	76	9	42
7c	Dichloromethane	30	68	9	40
7a	Chloroform	20	64	10	42
7b	Chloroform	25	68	10	45
7c	Chloroform	20	70	10	42

[a]*Time taken for the synthesis and Isolated yields after purification by microwave assisted method.*
[b]*Time taken for the synthesis and Isolated yields after purification by conventional method.*

RESULTS AND DISCUSSION

The most important method for the synthesis of thiazole is the reaction beween α-haloketones and thioamide. This method was established by hantzch and weber (1887) resultant to Hanzch thiazole synthesis. Here 4- formylpyrazole react with thiosemicarbazide in presence of catalytic amount of hydrochloric acid to yield thiosemicarbazone. Which on subsequent reaction with different substituted α-bromoketones afforded the 2-(2-((3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene) hydrazinyl) -4-sustitutedphenyl-2, 5-dihydrothiazole. Spectroscopic analysis (^{1}H NMR, ^{13}C NMR, IR, and MASS) of newly synthesised compound was agreement with planned structure. ^{1}H NMR of compound (4a) displayed the singlet at 2.32 δppm which indicate the methyle group proton, one singlet at 8.61 revels the -NH proton and proton resonate at 8.23 δppm as a singlet which is the aromatic ring proton nearest to nitro group. Thiazole ring proton merge with other aromatic proton at 7.20 δppm. The IR spectra of compound (4a) gives the stretching band at 3394 (-NH), 3132 (Aromatic), 2885(CH aliphatic), 1597, 1504 (NO_2), mass spectra gives the molecular ion peak at 480. All results are agreement with structure assigned.

Table 2. Synthesis of substituted thiazole derivatives by Microwave assisted method of synthesis

Entry	Structure	Molecular formula	Mass	Time[a] min.	% yield[b]	M.P. ^{0}C
7a		$C_{26}H_{20}N_6O_2S$	480.54	15	85	148-150
7b		$C_{25}H_{17}BrN_6O_2S$	545.41	15	80	152-154
7c		$C_{25}H_{17}ClN_6O_2S$	500.96	15	85	154-156
7d		$C_{26}H_{17}N_7O_2S$	491.52	20	70	160-162
7e		$C_{26}H_{20}N_6O_3S$	496.54	15	80	154-156
7f		$C_{25}H_{17}N_7O_4S$	511.51	20	70	168-170
7g		$C_{25}H_{18}N_6O_2S$	466.51	15	80	150-152
7h		$C_{25}H_{17}FN_6O_2S$	484.96	18	75	152-154

[a]*Time taken for the synthesis by microwave assisted method.*
[b]*Isolated yields after purification by microwave assisted method.*

For optimization of reaction, we have synthesized **7a, 7b** and **7c** in different solvents under microwave irradiation. We observed the higher yield within lesser time in the reaction which was carried out using methanol as solvent, instead of Dichloromethane, and Chloroform. The time taken for the completion of reaction under microwave assisted method was 15-20 minutes and observed the % yields was 70-85%. If we carried out the same synthesis under conventional method using methanol as solvent and piperidine as catalyst, the time taken for synthesis of **7a, 7b** and **7c** compounds was about 6 hours and the % yield observed was about 55-60%.

Characterization and Analytical data:

2-(2-((3-(3-Nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazinyl)-4-(p-tolyl) thiazole(7a).

MP 148-150°C; IR (KBr) cm^{-1}: 3394, 3132, 2885, 1705,1620, 1597, 1504, 1342, 817, 748, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.32 (s, 3H, CH_3), 4.86 (s, 1H), 7.21 (d, *J* = 9.8 Hz, 3H), 7.41 (t, *J* = 7.0 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 7.9 Hz, 2H), 7.84 (t, *J* = 7.9 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 2H), 8.23 (s, 1H), 8.33 (d, *J* = 7.6 Hz, 2H), 8.61 (s, 1H), 9.01 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 20.78. 38.80, 39.01, 39.22, 39.42, 39.63, 39.84, 40.05,102.71, 116.94, 118.73, 122.94, 122.94, 125.56, 127.16, 129.17, 129.63, 130.07, 130.86, 134.03, 135.00, 135.52, 135.52, 137.25, 138.74, 147.81, 148.16, 148.64, 149.05, 167.85, 167.85, Mass: [m/e (%)], M. Wt.: 480.14 Anal. Calcd. For $C_{26}H_{20}N_6O_2S$: C, 64.98; H, 4.20; N, 17.49; O, 6.66; S, 6.67; found: C, 64.40; H, 5.20; N, 17.60; O, 7.66.

4-(4-Bromophenyl)-2-(2-((3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) hydrazinyl) thiazole(7b).

MP 152-154°C; IR (KBr) cm^{-1}: 3300, 3122, 2880, 1710,1620, 1587, 1530, 1510, 1342, 820, 741, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.1 (s, 2H), 6.98 (s, 2H), 7.45 – 7.41 (m, 5H), 7.55 – 7.43 (m, 11H), 7.65 (s, 2H), 7.90 (s, 2H), 8.05 (s, 2H), 8.20 – 8.04 (m, 6H), 8.48 (s, 2H).^{13}C NMR (100 MHz, DMSO-d_6) δppm: 38.84, 39.05, 39.25, 39.46, 39.67, 39.88, 40.09, 104.28, 117.10, 118.72, 120.50, 122.49, 122.98, 127.12, 127.49, 129.64, 130.06, 131.48, 133.66, 134.11, 134.41, 135.01, 138.79, 147.82, 148.08, 148.95, 167.93. Mass: [m/e (%)], M. Wt.: 545.41 Anal. Calcd. For $C_{25}H_{17}BrN_6O_2S$: C, 55.05; H, 3.14; Br, 14.65; N, 15.41; O, 5.87; S, 5.88; found: C, 56.05; H, 3.18; N, 17.41; O, 6.67.

4-(4-Chlorophenyl)-2-(2-((3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4yl)methylene) hydrazinyl)thiazole(7c).

MP 154-156°C; IR (KBr) cm^{-1}: 3384, 3150, 2875, 1708, 1620, 1597, 1509, 1339, 815, 748, 643, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.60 (s, 1H), 7.40 – 7.31 (m, 3H), 7.51 – 7.44 (m, 2H), 7.61 – 7.42 (m, 4H), 7.65 (s, 1H), 7.95 (s, 1H), 8.05 (s, 1H), 8.21 – 8.04 (m, 3H), 8.51 (s, 1H), ^{13}C NMR (100 MHz, DMSO-d_6) δppm: 110.42, 120.95, 122.19, 124.64, 126.67, 128.80, 129.65, 129.69, 129.79, 129.80, 129.85, 129.89, 130.00, 130.17, 132.48, 133.98, 134.30, 134.59, 139.99, 143.78, 147.22, 148.64, 167.12, 168.98. Mass: [m/e (%)], M. Wt.: 500.96 Anal. Calcd. For $C_{25}H_{17}ClN_6O_2S$: C, 59.94; H, 3.42; Cl, 7.08; N, 16.78; O, 6.39; S, 6.40; found: C, 59.60; H, 3.12; N, 16.90; O, 7.39.

4-(2-(2-((3-(3-Nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazinyl)thiazol-4-yl)benzonitrile(7d).

MP 160-162°C; IR (KBr) cm^{-1}: 3404, 3122, 2890, 1710,1620, 1597, 1514, 1341, 820, 722, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.62 (s, 1H), 7.43 (s, 1H), 7.52 – 7.46 (m, 2H), 7.60 – 7.48 (m, 2H), 7.68 (s, 1H), 7.75 – 7.65 (m, 2H), 7.85 – 7.76 (m, 2H), 7.94 (s, 1H), 8.04 (s, 1H), 8.14 (s, 1H), 8.19 (d, *J* = 6.1 Hz, 2H), 8.53 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δppm: 111.43, 114.59, 116.19, 119.80, 122.19, 122.54, 127.27, 127.91, 127.91, 129.03, 129.50, 129.68, 129.84, 130.17, 132.45, 134.40, 136.78, 139.90, 143.89, 146.21, 149.64, 167.92, 168.00. Mass: [m/e (%)], M. Wt.: 491.52 Anal. Calcd. For $C_{26}H_{17}N_7O_2S$: C, 63.53; H, 3.49; N, 19.95; O, 6.51; S, 6.52; found: C, 64.53; H, 3.80; N, 20.95; O, 7.51.

4-(4-Methoxyphenyl)-2-(2-((3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) hydrazinyl)thiazol(7e).

MP 154-156°C; IR (KBr) cm^{-1}: 3389, 3125, 2895, 1712,1620, 1597, 1510, 1382, 836, 748, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 3.71 (s, 3H), 5.86 (s, 1H), 6.29 (s, 1H), 6.80 (d, *J* = 8.5 Hz, 3H), 7.06 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.27 (m, 5H), 7.60 (t, *J* = 7.3 Hz, 2H), 7.91 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 38.82, 39.03, 39.24, 39.45, 39.66, 39.87, 40.07, 104.21, 117.08, 118.71, 122.96, 127.20, 128.57, 129.62, 130.05, 131.95, 133.17, 134.09, 134.60, 134.99, 138.77, 139.07, 147.81, 148.07, 148.67, 152.70, 167.94. Mass: [m/e (%)], M. Wt.: 496.54 Anal. Calcd. For $C_{26}H_{20}N_6O_3S$: C, 62.89; H, 4.06; N, 16.93; O, 9.67; S, 6.46; found: C, 61.89; H, 5.06; N, 17.93; O, 9.66.

4-(4-Nitrophenyl)-2-(2-((3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) hydrazinyl)thiazole(7f).

MP 168-170°C; IR (KBr) cm^{-1}: 3398, 3138, 2879, 1711,1625, 1598, 1515, 1342, 820, 718, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.70 (s, 1H), 7.42 (s, 1H), 7.50 – 7.44 (m, 2H), 7.61 – 7.50 (m, 2H), 7.63 (s, 1H), 7.92 – 7.78 (m, 2H), 8.06 – 7.92 (m, 3H), 8.18 (s, 1H), 8.34 – 8.20 (m, 2H), 8.51 (d, *J* = 1.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 111.41, 119.03, 120.12, 120.89, 121.19, 121.54, 126.09, 126.27, 127.12, 127.79, 128.03, 129.18, 129.75, 129.80, 130.07, 131.45, 133.30, 137.07, 138.97, 141.98, 145.22, 147.03, 149.64, 160.12, 167.78. Mass: [m/e (%)],

M. Wt.: 511.51 Anal. Calcd. For $C_{25}H_{17}N_7O_4S$: C, 64.36; H, 3.89; N, 18.01; O, 6.86; S, 6.87; found: C, 65.36; H, 3.92; N, 19.01; O, 8.86.

2-(2-((3-(3-Nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)hydrazinyl)-4-pheny lthiazole(7g).
MP 150-152°C; IR (KBr) cm^{-1}: 3386, 3133, 2881, 1716,1622, 1597, 1508, 1341, 826, 720, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.65 (s, 1H), 7.29 (s, 1H), 7.39 (t, *J* = 9.1 Hz, 3H), 7.52 – 7.46 (m, 2H), 7.59 – 7.51 (m, 2H), 7.71 – 7.60 (m, 3H), 8.96 (s, 1H), 8.06 (s, 1H), 8.22 – 8.12 (m, 3H), 8.54 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 109.11, 118.59, 120.12, 120.97, 123.19, 123.54, 124.78, 127.28, 127.31, 127.91, 129.03, 129.50, 129.71, 129.80, 131.17, 131.45, 133.30, 136.77, 138.77, 141.98, 145.22, 146.03, 148.64, 163.12, 169.98. Mass: [m/e (%)], M. Wt.: 466.51 Anal. Calcd. For $C_{25}H_{18}N_6O_2S$: C, 64.36; H, 3.89; N, 18.01; O, 6.86; S, 6.87; found: C, 64.46; H, 3.92; N, 18.08; O, 6.90.

4-(4-Fluorophenyl)-2-(2-((3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) hydrazinyl)thiazole(7h).
MP 152-154°C; IR (KBr) cm^{-1}: 3389, 3135, 2868, 1735,1622, 1597, 1504, 1341, 836, 744, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 6.62 (s, 1H), 7.11 (t, *J* = 7.8 Hz, 2H), 7.49 – 7.38 (m, 3H), 7.68 – 7.50 (m, 5H), 7.92 (s, 1H), 8.04 (s, 1H), 8.21 – 8.11 (m, 3H), 8.51 (t, *J* = 1.5 Hz, 1H), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 109.11, 119.99, 118.12, 118.65, 120.19, 121.54, 124.91, 125.27, 127.31, 127.91, 127.03, 128.48, 129.70, 129.90, 131.17, 132.45, 134.40, 136.77, 139.97, 144.98, 146.27, 148.07, 148.64, 163.62, 168.98. Mass: [m/e (%)], M. Wt.: 484.11 Anal. Calcd. For $C_{25}H_{17}FN_6O_2S$: C, 61.97; H, 3.54; F, 3.92; N, 17.35; O, 6.60; S, 6.62, found: C, 61.80; H, 3.60; N, 17.38; O, 6.70.

CONCLUSION

A convenient synthetic route has been developed for the cyclocondensation reaction between α-haloketons and thioamide, which gives the thiazole in excellent yield. The evidences of this microwave assisted method are efficient methodology, excellent yields, cleaner reaction profiles, simple work-up method and lesser reaction time.

Acknowledgements
The authors are gratified to Department of Chemistry, Saurashtra University, Rajkot and specially appreciative to "National Facility for Drug Discovery through New Chemical Entities (NCE's) (Centre of Excellence), Development & Instrumentation Support to Small Manufacturing Pharma Enterprises", a programme under Drug & Pharma Research Support (DPRS) jointly funded by Department of Science & Technology, New Delhi, Government of Gujarat (Industries Commissionerate) & Saurashtra University, Rajkot.

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