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Synthesis of new thiazolylmethoxyphenyl pyrimidines and antihyperglycemic evaluation of the pyrimidines, analogues isoxazolines and pyrazolines

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ABSTRACT

New thiazolylmethoxyphenyl pyrimidines (**7a**–**g**) have been conveniently synthesized with better yields by cyclocondensing 3-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-1-(4-substituted phenyl)prop-2-en-1-ones (**4a**–**g**) with thiourea in aqueous emulsion of tetradecyltrimethylammonium bromide (TTAB) at 80 °C. Antihyperglycemic activity of the new thiazolylmethoxyphenyl pyrimidines (**7a**–**d**), thiazolylmethoxyphenyl pyrazolines (**5a**–**d**) and thiazolylmethoxyphenyl isoxazolines (**6a**–**d**) has been evaluated in sucrose loaded rat model. Among these compounds; **5a**, **5c**, **6b**, **7c** and **7d** have displayed noticeable antihyperglycemic activity. Pyrimidines and pyrazolines have displayed better antihyperglycemic activity than the analogues isoxazolines.

Diabetes mellitus is a metabolic disorder of multiple etiologies.[1] Type II is the most common form of diabetes and accounts for approximately 80–90% of all cases of diabetes and it is the fastest growing global threat to public health.[2] Hyperglycemia or raised blood sugar is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves, eyes, kidney and blood vessels.[3] Metoformin, sulfonylureas, thiazolidinediones (TZDs) and DPP IV inhibitors are the most widely used antidiabetic/antihyperglycemic agents in clinical situations.[4] It is still difficult to strongly control plasma glucose and prevent diabetic complications. So there is urgent need to focus attention on novel pharmaco therapy which will be able to achieve glycemic control singly or to be used with the existing agents, more safely.

Therefore now attention is found to be directed on designing and developing new sulfonylureas, biguanidines, thiazolidinediones bearing biodynamic sulfur/nitrogen containing heterocyclic rings. Recently heterocycles, viz thiazoles, pyrimidines, pyrazolines, isoxazolines have been assessed for their antidiabetic activities.[5,6] Structure activity relationship studies of 2,4,6-trisubstituted-5-pyrimidine carboxylic acids have shown that these products are PPARγ agonist.[7] It has been reported that novel 3,5-diaryl pyrazolines act as low-density lipoprotein (LDL) oxidation inhibitor.[8] Isoxazolines are known for their hypoglycemic activity. Some of the new benzofuran isoxazolines are found to have antihyperglycemic activity.[9] Thiazolyl pyrazoles act as glucokinase (GK) activator.[10] Ethereal linkage is also one of the necessities of molecule to display antidiabetic activity and is present in various antidiabetic drugs, pioglitazone and rosiglitazone.[11]

The clinically used antihyperglycemic agents, thiazolidinedione analogues are having essentially an acidic head group, a central phenyl ring and a hydrophobic tail group joined by ethereal linkage.[12] Several modifications have been attempted in the tail and head groups toward developing more potent and safer antihyperglycemic agents.[13–16] The structural modifications carried out in the head and tail portions via substitutions like thiazoles and oxazoles,[17] indinone,[18] indolyl acetic acid,[19] oxazolidinediones and isoxazolidinediones moieties.[20] Many of these modified compounds have displayed interesting antihyperglycemic activity, showing that modifications at either site could modulate the antidiabetic activity.

In view of the need of potent and safe antidiabetic agents and in continuation of our earlier interest in this field,[21] here it was planned to synthesize new analogues by introducing thiazole ring system at tail and pyrimidines/pyrazolines/isoxazolines at head retaining ethereal linker with expectation to obtain the new products with better antihyperglycemic activity.

Recently we have reported the multistep synthesis of thiazolylmethoxyphenyl pyrazolines (**5a**–**d**) and thiazolylmethoxyphenyl

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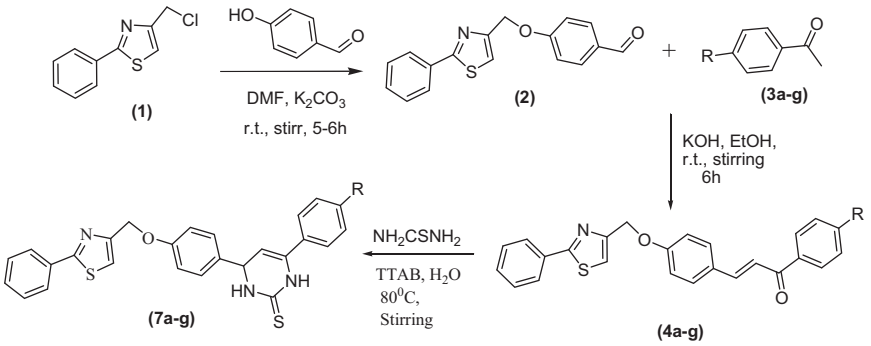


Scheme 1. Synthesis of thiazolylmethoxyphenyl pyrimidines (**7a**–**g**).

Table 1
Physical data of 4-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-3,4-dihydro-6-*p*-substituted pyrimidine-2-thiones (**7a**–**g**)[a]

Entry	Compound	R	Yield[b] (%)	Melting point (°C)
1	**7a**	–H	71	158–160
2	**7b**	$-OCH_3$	73	88–90
3	**7c**	–F	68	82–84
4	**7d**	$-NO_2$	70	87–89
5	**7e**	–Br	65	83–85
6	**7f**	$-CH_3$	60	94–96
7	**7g**	3,5-Di F	62	81–82

[a] Reaction conditions: 2-propene-1-ones (2 mmol), thiourea (2 mmol), sodium ethoxide (2 mmol) TTAB (15 mol %), water(10 ml), stirred at 80 °C for 5 h.
[b] Isolated yields.

Table 2
Effect of compounds **5a**–**d**, **6a**–**d**, **7a**–**d** and standard antidiabetic drug metformin on oral sucrose tolerance (OSTT) in post sucrose loaded normal rats

S. No.	Compounds	Dose (mg/kg)	% improvement on OSTT	Significance
1	**5a**	100	**7.42***	p <0.05
2	**5b**	100	+0.85	—
3	**5c**	100	**10.4****	p <0.01
4	**5d**	100	2.47	—
5	**6a**	100	2.73	—
6	**6b**	100	**8.37****	p <0.01
7	**6c**	100	4.88	—
8	**6d**	100	0.91	—
9	**7a**	100	0.07	—
10	**7b**	100	1.05	—
11	**7c**	100	**8.22***	p <0.05
12	**7d**	100	**7.04***	p <0.05
13	Metformin	100	**14.1**	p <0.01

Compounds are with bold and asterisk shows the significant activity.

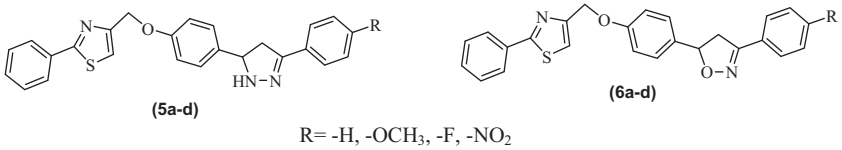
isoxazolines (**6a**–**d**) using 4-chloromethyl thiazole as starting material (Figure 1).[22] However the antidiabetic/antihyperglycemic evaluation of these was not then reported. Therefore herein we report the synthesis of new thiazolylmethoxyphenyl pyrimidines (**7a**–**g**) and antihyperglycemic screening results of the thiazolylmethoxyphenyl pyrimidines (**7a**–**d**), pyrazolines (**5a**–**d**) and isoxazolines (**6a**–**d**).

By following our reported protocol, here synthesis of new thiazolylmethoxyphenyl pyrimidines was achieved by cyclocondensing 3-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-1-(4-substituted phenyl)prop-2-en-1-ones (**4a**–**g**) with thiourea in aqueous emulsion of TTAB as illustrated in Scheme 1. The required precursors, 2-propen-1-ones (**4a**–**g**) were freshly prepared starting from 4-((2-phenylthiazol-4-yl)methoxy)benzaldehyde (**2**) with quantitative yield. 4-((2-Phenylthiazol-4-yl)methoxy)benzaldehyde (**2**) was synthesized by allowing the interaction of chloromethylthiazole (**1**) with 4-hydroxybenzaldehyde in *N*,*N*-dimethyl formamide in the presence of K_2CO_3. The Claisen–Smith condensation of the aldehyde (**2**) and various acetophenones (**3a**–**g**) when carried in ethanol in presence of KOH at room temperature gave 3-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-1-(4-fluorophenyl)prop-2-en-1-ones (**4a**–**g**) with good to better yields (Scheme 1) and their melting points are in good agreement with those reported.[22]

An environmental benign and eco sustainable synthetic protocol has been developed for the synthesis of new 4-(4-((2-phenylthiazol-4-yl)methoxy)phenyl)-3,4-dihydro-6-*p*-substituted pyrimidine-2-thiones (**7a**–**g**) by separately condensing thiourea with the 2-propen-1-ones (**4a**–**g**) in water in the presence of TTAB at 80 °C (Table 1). The role of aqueous emulsion of surfactant in rate acceleration of organic transformations is well established.[23] The catalytical behaviour of aqueous micellar TTAB in these cyclocondensations can be explained as follows:

2-Propene-1-ones (**4a**–**g**) react with thiourea to yield the titled heterocycles. The substrates and the reagents used in these cyclocondensations are major hydrophobic forms and therefore water insoluble. TTAB micellar emulsion is having micellar hydrophobic cavities. These hydrophobic cavities are responsible to solubilise the substrates, 2-propene-1-ones and thiourea. This is because of repulsive push by water, these enter into hydrophobic core of micellar droplets and that enhances concentration of substrates and the nucleophilic reagent, thiourea in the hydrophobic cavities. This high localize homogenous concentration of the reactants might be helping into rate acceleration of the cyclocondensation.

All the synthesized compounds have been characterized using their IR, ^{1}H NMR, ^{13}C NMR, and Mass spectral data.[24] The IR spectrum of compound, **7a** indicates the formation of the product as it shows a characteristic absorptions at 3410, 1,512 and 1242 cm^{-1}



R= -H, $-OCH_3$, -F, $-NO_2$

Figure 1. Thiazolylmethoxyphenyl pyrazolines (**5a**–**d**) and thiazolylmethoxyphenyl isoxazolines (**6a**–**d**).