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One-Pot Multicomponent Synthetic Route for New Quinolidinyl 2,4-Thiazolidinediones

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A convenient one-pot condensation route has been developed for obtaining 5-[(2-(piperidin-1-yl) quinolin-3-yl) methylene]-2,4-thiazolidinediones using multicomponents, 2-chloro-3-formyl quinolines, piperidine, 2,4-thiazolidinedione and safer medium/mediator, polyethylene glycol-400.

Key Words: Polyethylene glycol-400, Quinolidinyl 2,4-thiazolidinediones, One-pot synthesis

Introduction

Thiazolidine and its derivatives are an important class of bioactive heterocycles.[1] The subtype, 2,4-thiazolidinedione class has displayed promising pharmacological activities.[2] A number of 2,4-thiazolidinedione based molecules such as, troglitazone,[3] englitazone,[4] pioglitazone[5] and rosiglitazone[6] have shown potential activities and are used as clinical *anti*-diabetic agents.

Quinolines are gaining importance in medicinal and natural product chemistry[7] due to their interesting biological and pharmacological activities such as, *anti*-malarial, *anti*-tuberculosis, *anti*-inflammatory and *anti*-cancer.[8] It is also revealed that the heteryl substituents on 2,4-thiazolidinedione activate the ring systems.[9] The combination of quinoline and 2,4-thiazolidinedione in a molecular framework has shown remarkable euglycemic and hypolipidemic activities.[9]

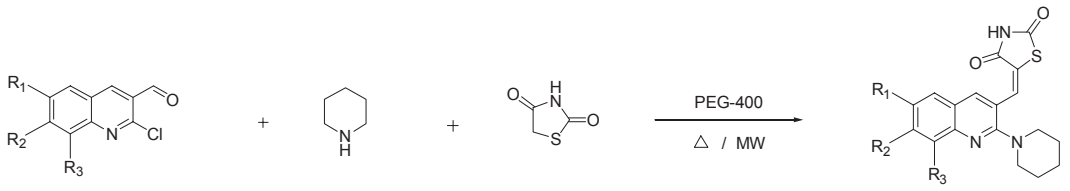
There is no report on the synthesis of 2,4-thiazolidinediones bearing heteryl substituents like, piperidinyl quinolines. Keeping the above potent usefulness of the heterocycles in mind, here it was thought worthwhile to synthesize the titled, new quinolidinyl 2,4-thiazolidinediones with hope to obtain the molecules with potential hypoglycemic activity by developing a convenient synthetic route using readily available starting materials.

It has also been reported[10] that 2-chloro-3-fomyl quinolines can be separately condensed with secondary amines and substrate bearing active methylene groups like malononitrile/ barbituric acid etc. neatly or using trimethylsilyl chloride in dimethylformamide (DMF) and obtained moderate yields of the products.

In continuation of our earlier interest[11] to synthesize new analogues of bioactive 2,4-thiazolidinediones, here an attempt is made to synthesize the titled products by overcoming the limitations of the condensations and developed one-pot multicomponent synthetic route. The multicomponent reactions approach was considered because of its wide range of advantages and exceptional synthetic efficiency.[12]

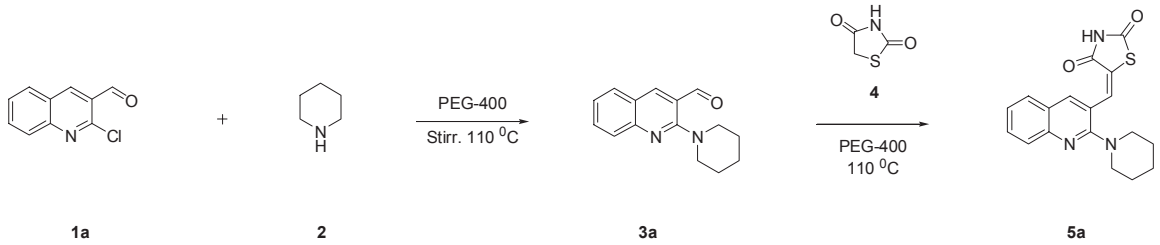
Results and Discussion

To develop one-pot multicomponent route for the titled products, we first focused on optimization of the reaction conditions using readily available materials. The model/reference reaction of 2-chloro-3-formyl quinoline (**1a**) was carried using a mixture of piperidine (**2**) and 2,4-thiazolidinedione (**4**) in solvents like dimethylformamide (DMF) and water at reflux conditions. It was noticed that, this condensation didn't result into desired product, 5-[(2-(piperidin-1-yl)quinolin-3-yl)methylene]-2,4-thiazolidinedione (**5a**). However, the product was found to be *N*-alkylated, 2-(piperidin-1-yl)quinoline-3-carbaldehyde (**3a**) which clearly indicated that there was no further Knoevenagel condensation between the intermediate, 2-(piperidin-1-yl)quinoline-*3*-carbaldehyde (**3a**) and 2,4-thiazolidinedione (**4**). To overcome this limitation in another effort 2-chloro-3-formyl quinoline (**1a**) was allowed to interact with mixture of piperidine (**3**) and 2,4-thiazolidinedione (**4**) in polyethylene glycol-400 at 110 °C. It was noticed that, nucleophilic displacement of chlorine and the successive Knoevenagel condensation had occurred in one-pot resulting into the desired product, 5-[(2-(piperidin-1-yl)quinolin-3-yl)methylene]-2,4-thiazolid inedione (**5a**) (Scheme 1).



1a-g **2** **4** **5a-g**

Scheme 1



Scheme 2

Table 1. Physical data of the synthesized compounds **5a-g**

Entry	R_1	R_2	R_3	Products	Reaction Time		Yields[a] (%)		mp. (°C)
					A (h)	B (min)	A	B	
1	H	H	H	**5a**	8	7	72	75	245 - 247
2	$-OC_2H_5$	H	H	**5b**	9	7	70	72	260 - 262
3	$-OCH_3$	H	H	**5c**	8	7	70	72	270 - 272
4	$-CH_3$	H	H	**5d**	8	8	69	71	276 - 278
5	H	$-OCH_3$	H	**5e**	9	7	69	70	201 - 203
6	H	$-CH_3$	H	**5f**	9	8	68	70	221 - 223
7	H	H	$-C_2H_5$	**5g**	9	8	65	67	218 - 220

[a]Isolated yields after column chromatography technique. A: Conventional heating 110 °C; B: Microwave heating 540 W (110 °C).

To know the synthetic sequences first 2-chloro-3-formyl quinoline (**1a**) was condensed with piperidine (**2**) in polyethylene glycol-400 and the isolated *N*-alkylated product 2-(piperidin-1-yl)quinoline-3-carbaldehyde (**3a**) was then allowed to interact with 2,4-thiazolidinedione (**4**) in polyethylene glycol-400 at 110 °C. After completion of the reaction the isolated product was found to be 5-[(2-(piperidin-1-yl)quinolin-3-yl methylene]-2,4-thiazolidinedione (**5a**) (Scheme 2).

It was therefore, confirmed that in one-pot condensation of 2-chloro-3-fomyl quinoline, piperidine and 2,4-thiazolidinedione, *N*-alkylation would have been initially occurred and it would have followed by Knoevenagel condensation between the intermediate *N*-alkylated, 2-(piperidin-1-yl)quinoline-3-carbaldehyde (**3a**) and that of 2,4-thiazolidinedione (**4**). The time required for this one-pot condensation was found to be relatively less than two step route.

The rate acceleration might be because of homogenous mass and high concentration of the reactants in polyethylene glycol-400. The rate enhancement can also be attributed to phase transfer catalytical behavior of polyethylene glycol-400. The terminal hydroxyl groups of PEG would also be participating in H-bonding with carbonyl oxygen of the intermediate, 2-(piperidin-1-yl)quinoline-3-carbaldehyde, enhancing the electrophilicity of aldehydic carbon.

The time required in one-pot condensation was between 8 - 9 h when carried at 110 °C using thermal heating. Further to expedite the condensation the mixture of 2-chloro-3-formyl quinoline (**1a**), piperidine (**2**) and 2,4-thiazolidinedione (**4**) was dissolved in minimum volume of polyethylene glycol-400 and the reaction solution was irradiated under microwave at 110 °C using 540 W. It was recorded that the successive condensations occurred within 7 - 8 min giving better yields of the titled products (**5a**).

After optimizing the reaction conditions, we examined the scope and generality of this method using variety of substituted 2-chloro-3-formyl quinolines (**1a-g**), piperidine and 2,4-thiazolidinedione in PEG-400 by carrying them separately under the thermal and microwave energy sources. These results are summarized in Table 1 and the spectral data is incorporated in the experimental section.

Conclusion

The one-pot multicomponent protocol developed for the obtaining titled products, quinolidinyl 2,4-thiazolidinediones require moderate reaction conditions and is accompanying with economic yields. The PEG-400 used in the procedure is safer medium/catalyst and recyclable one. The use of microwave irradiation in acceleration of the condensations is worth noted. The isolation of the pure products is not tedious. Therefore, it is claimed that we have developed a convenient one-pot multicomponent high yielding route for the titled products and thus introduced bioactive piperidinyl quinolidinyl moiety into 2,4-thiazolidinediones.

Experimental

All chemicals and solvents were purchased from Spectrochem and S. D. Fine-chem. (India). All the melting points were recorded by open capillary method and are uncorrected. The reactions were carried out in a Milstone MicroSYNTH Labstation for Synthesis, MW oven having a maximum power output of 1200 W. IR spectra were recorded on JASCO FT-IR 4100, Japan by using KBr discs. ^{1}H NMR and ^{13}C NMR spectra were

recorded with a Bruker Avance 400 spectrometer operating at 400 MHz and 100 MHz using $CDCl_3$ or DMSO-d_6 solvent and tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded on Single-Quadrupole Mass Detector 3100, Waters. The observed molecular ions are having 1 amu higher *m*/*z* in the spectra than the expected.

Two step synthesis of 5-[(2-(piperidin-1-yl)quinolin-3-yl methylene]-2,4-thiazolidinedione (5a).

A) Synthesis of 2-(piperidin-1-yl)quinoline-3-carbaldehyde (3a): 2-Chloro-3-formyl quinoline (**1a**) (10 mmol) and piperidine (**2**) (11 mmol) were dissolved in polyethylene glycol-400 (10 mL) and the reaction solution was stirred at 110 °C for 2 h. The progress of the reaction was monitored by TLC using hexane-ethyl acetate (7:3). After completion of reaction, the reaction mass was cooled and poured on ice water and extracted with diethyl ether. The ethereal extract was evaporated under rotary vacuum. The crude product thus obtained was then purified by column chromatography (hexane-ethyl acetate). Yellow solid; mp 83 - 84 °C. The melting point of the product is in good agreement with that reported in the literature.[10b]

B) Synthesis of 5-((2-(piperidin-1-yl)quinolin-3-yl)methylene)thiazolidine-2,4-dione (5a): A mixture of 2-(piperidin-1-yl) quinoline-3-carbaldehyde (10 mmol) (**3a**) and 2,4- thiazolidinedione (**4**) (10 mmol) was dissolved in polyethylene glycol-400 (10 mL) and the solution was stirred at 110 °C for 8 h. The progress of the reaction was monitored by TLC using hexane-ethyl acetate (7:3). After completion of reaction, the reaction mass was cooled and poured on ice water and extracted with diethyl ether. The ethereal extract was evaporated under rotary vacuum. The crude product thus obtained was then purified by column chromatography. Yellow solid, mp 245 - 247 °C.

One-pot synthesis of 5-((substituted 2-(piperidin-1-yl)quinolin-3-yl)methylene) -2,4-thiazolidnediones (5a-g).

A) Thermal route: A mixture of substituted 2-chloro-3-formyl quinoline (**1a**) (10 mmol), piperidine (**2**) (20 mmol) and 2,4-thiazolidinedione (**4**) (10 mmol) were dissolved in polyethylene glycol-400 (10 mL), and the reaction mixture was stirred at 110 °C for 8 - 9 h. The progress of the reaction was monitored by TLC using hexane-ethyl acetate (7:3). After completion of reaction, the reaction mass was cooled and poured on ice water and extracted with diethyl ether. The ethereal extract was evaporated under rotary vacuum. The crude product thus obtained was then purified by column chromatography.

B) Microwave irradiation route: A mixture of substituted 2-chloro-3-formyl quinoline (**1a**) (10 mmol), piperidine (**2**) (20 mmol) and 2,4- thiazolidinedione (**4**) (10 mmol) were dissolved in polyethylene glycol-400 (5 mL). The reaction mixture was then exposed to 540 W at 110 °C for 7 - 8 min. After completion of reaction, the reaction mass was cooled and poured on ice water and extracted with diethyl ether. The ethereal extract was evaporated under rotary vacuum. The crude product thus obtained was then purified by column chromatography.

5-((2-(Piperidin-1-yl)quinolin-3-yl)methylene)-2,4-thiazolidnedione (5a): Yellow solid, mp 245 - 247 °C, IR (KBr, cm^{-1}) 3307, 2931, 1723, 1688, 1566 and 1376. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.60-1.67 (m, 6H, 3-CH_2, overlapped piperidinyl-H), 3.22-3.31 (m, 4H, 2-CH_2, piperidinyl-H), 7.01 (s, 1H, vinylic-H), 7.64-8.26 (m, 5H, Ar-H), 12.26 (s, 1H, -NH exchangeable with D_2O). ^{13}C NMR (100 MHz, DMSO-d_6) 23.58, 24.88, 50.80, 120.26, 123.17, 123.47, 123.80, 136.20, 146.43, 159.06, 166.04, 166.81, 170.00. ESI-MS (*m*/*z*) 340 (M^+).

5-((6-Ethoxy-2-(piperidin-1-yl)quinoline-3-yl)methylene)-2,4-thiazolidinedione (5b): Reddish brown solid, mp 260 - 262 °C, IR (KBr, cm^{-1}) 3408, 3038, 1743, 1687, 1581 and 1323. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41 (t, 3H), 1.69 (m, 6H, 3-CH_2, overlapped piperidinyl-H), 3.18 (m, 4H, 2-CH_2, piperidinyl-H), 4.04 (q, 2H), 6.94 (s, 1H, Vinylic-H), 7.22-7.95 (m, 4H, Ar-H), 12.08 (s, 1H, -NH exchangeable with D_2O): ^{13}C NMR (100 MHz, DMSO-d_6) 14.25, 23.99, 25,36, 29.07, 51.54, 63.11, 105.87, 122.78, 124.03, 124.38, 128.30, 129.06, 135.03, 142.60, 155.20, 158.47, 166.93, 167.47, 169.00. ESI-MS (*m*/*z*) 384 (M^+).

5-((6-Methoxy-2-(piperidin-1-ylquinolin-3-ylmethylene)-2,4-thiazolidnedione (5c): Yellow solid, mp 270 - 272 °C, IR (KBr, cm^{-1}) 3411, 3035, 1742, 1688, 1578 and 1326. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (m, 6H, 3-CH_2, overlapped piperidinyl-H), 2.90 (m, 4H, 2-CH_2, piperidinyl-H), 3.75 (s, 3H), 6.76 (s, 1H, vinylic-H), 7.01-7.77 (m, 4H, Ar-H) 11.9 (s, 1H, -NH exchangeable with D_2O). ESI-MS (*m*/*z*) 370 (M^+).

5-((6-Methyl-2-(piperidin-1-yl)quinolin-3-yl)methylene)-2,4-thiazolidnedione (5d): Yellow Solid, mp 276 - 278 °C, IR (KBr, cm^{-1}) 3367, 3027, 1743, 1688, 1587 and 1381. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68 (m, 6H, 3-CH_2, overlapped piperidinyl-H), 2.78 (m, 4H, 2-CH_2, piperidinyl-H), 3.27 (s, 3H), 7.13 (s, 1H, vinylic-H), 7.42-8.00 (m, 4H, Ar-H), 12.07(s, 1H, -NH exchangeable with D_2O). ESI-MS (*m*/*z*) 354 (M^+).

5-((7-Methoxy-2-(piperidin-1-yl)quinolin-3-yl)methylene)-2,4-thiazolidnedione (5e): Brown reddish solid, mp 201 - 203 °C, IR (KBr, cm^{-1}) 3411, 3035, 1745, 1670, 1580 and 1326. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (m, 6H, 3-CH_2, overlapped piperidinyl-H), 2.90 (m, 4H, 2-CH_2, piperidinyl- H), 3.75 (s, 3H), 6.80 (s, 1H, vinylic-H), 7.00-7.90 (m, 4H, Ar-H) 12.0 (s, 1H, -NH exchangeable with D_2O). ESI-MS (*m*/*z*) 370 (M^+).

5-((7-Methyl-2-(piperidin-1-yl)quinolin-3-yl)methylene)-2,4-thiazolidnedione (5f): Yellow solid, mp 221 - 223 °C, IR (KBr, cm^{-1}) 3367, 3027, 1744, 1689, 1585 and 1380. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.55 (m, 6H, 3-CH_2, overlapped piperidinyl-H), 2.80 (m, 4H, 2-CH_2, piperidinyl-H), 3.10 (s, 3H), 7.10 (s, 1H, vinylic-H), 7.10-8.00 (m, 4H, Ar-H), 12.07(s, 1H, -NH exchangeable with D_2O). ESI-MS (*m*/*z*) 354 (M^+).

5-((8-Ethyl-2-(piperidin-1-yl)quinolin-3-yl)methylene)-2,4-thiazolidnedione (5g): Yellow solid, mp 218 - 220 °C, IR (KBr, cm^{-1}) 3367, 3027, 1741, 1680, 1590 and 1382. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24 (t, 3H), 1.60 (m, 6H, 3-CH_2, overlapped piperidinyl-H), 2.50 (q, 2H), 2.78 (m, 4H, 2-CH_2, piperidinyl-H), 6.98 (s, 1H, vinylic-H), 7.07-7.88 (m, 4H, Ar-H), 12.00 (s, 1H, -NH exchangeable with D_2O). ESI-MS (*m*/*z*) 368 (M^+).

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