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Articles

Synthetic Route for New (*Z*)-5-[4-(2-Chloroquinolin-3-yl) Methoxy]benzylidinethiazolidine-2,4-diones

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Synthetic route has been developed for the synthesis of new (*Z*)-5-[4-(2-chloroquinolin-3-yl) methoxy]benzylidinethiazolidine-2,4-diones (**6a-h**) starting from 2-chloro-3-hydroxymethyl quinolines (**2a-h**). The hydroxy methyl quinolines on tosylation yielded (**3a-h**). Condensation of the tosyl intermediates with 4-hydroxy benzaldehydes has been carried in DMF in presence of K_2CO_3 and obtained 4-quinolinyl methoxy benzaldehydes (**4a-h**). Conveniently Knoevenagel condensation of quinolinyl methoxy benzaldehydes (**4a-h**) and 2, 4-thiazolidinedione (**5**) has been carried in PEG-400 in presence of L-proline and obtained better yields of the titled compounds (**6a-h**).

Key Words : 2,4-Thiazolidinedione, Quinoline, L-Proline, PEG-400, Etheral linkage

Introduction

2,4-Thiazolidinediones (TZD's) display elegant pharmacological properties.[1] Type 2 diabetes mellitus has been revolutionized with the advent of 2,4-thiazolidinediones.[2] TZD's are also known as a group of peroxisome proliferator activator gamma receptors (PPAR gamma).[3] TZD's scaffold has been found as core nucleus in various antidiabetic drugs[4] viz., pioglitazone, rosiglitazone, KRP-297, lobiglitazone and DRF-2189. 5-Arylidenyl 2,4-thiazolidinediones have also displayed potential phospholipase A2 inhibitor, dual COX-2/5-LOX inhibitor and anti-inflammatory activities.[5]

Structural Activity Relationship (SAR) studies on 2,4-thiazolidinediones have shown that the substituent at 5th position of the 2,4-thiazolidinedione ring system influences the pharmacological activities.[6] Knoevenagel condensation of 2,4-thiazolidinediones and aldehydes has found to be one of the key steps in the syntheses of clinically used hypoglycemic agents. Ethereal linkage is found to be necessary component in the molecular framework of various antidiabetic agents.[4]

Quinoline is one of the privileged medicinal scaffold due to its elegant pharmacological properties like antibacterial,[7] antidepressant[8] antimalerial[9] and hypoglycemic.[10]

In view of the pharmacological importance of 2,4-thiazolidinediones, quinolines and ethereal linkages and drawbacks associated with the reported methods, here it was thought worthwhile to construct some new 5-((4-((2-chloroquinolin-3-yl) methoxy) phenyl) methylene) thiazolidine-2, 4-diones with the hope to obtain the compounds with intensified activities.

To construct the titled/desired products here attempts have been made to provide convenient synthetic route starting from known and readily available reactants like 2-chloro-3-formyl-quinolines and 2,4-thiazolidinedione. 2-Chloro-3-formyl quinolines, prepared by literature route[11] have been successfully converted to new aldehydes, 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes, (**4a-h**) by following the steps depicted in Scheme 1. Using these new aldehydes titled compounds have been synthesized employing convenient reaction conditions.

Literature reveals that there are various reports dealing with the Knoevenagel condensations of various aldehydes and 2,4-thiazolidinediones, carried in organic medium using catalysts like zeolite,[12] alum,[13] piperidine in ethanol,[14] piperidine and benzoic acid in toluene,[15] piperidine benzoate in toluene,[16] and soluble polymer.[17]

In an initial attempt the Knoevenagel condensation of the new aldehydes (**4a-h**) and 2,4-TZD has been carried by varing catalysts and reaction media. The condensation was even carried in the absence of catalysts. In all these attempts it was observed that it did not run satisfactorily.

The known protocols to run the Knoevenagel condensations have been found to have drawbacks like need of toxic, hazardous and flammable media and expensive catalysts. It has also been noted that they did not work for the condensations under reference, therefore it was thought to provide a convenient and safe protocol for the Knoevenagel condensation using some of the green tools.

PEG-400 being safer medium and catalyst here the above condensation was run in PEG-400 at 130 °C. It was noted that the condensation was not completed even after prolong heating. To accelerate the rate of the condensation in PEG-400 various catalysts were tried. It was found that the

condensation of 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes, (**4a-h**) and 2,4-thiazolidinedione in PEG-400 has been found to be successfully proceeded when carried in presence of L-proline at 60 °C and gave moderate yields of the titled products. The details of the optimization of the reaction conditions of the Knoevenagel condensation and the other steps involved in the synthesis of new aldehydes, (**4a-h**) have been recorded in the result and discussion part.

Experimental Section

Chemicals and solvents required were procured from Merck, Spectorchem and S.D fine chem. ^{1}H-NMR spectra were recorded on Jeol and Bruker DRX-300 at 400 MHz and 300 MHz, respectively. The mass spectra were recorded on Shimanzu GCMS and JEOL-Accu TOF DART-MS-T 100Lc. Elemental analyses were screened on EA1108 (Carlo-Erba). The melting points were taken in open capillary and are uncorrected.

Experimental Procedure for the Synthesis of (*Z*)-5-[4-(2-Chloroquinolin-3-yl) Methoxy] benzylidinethiazolidine-2,4-diones. A mixture of 4-((2-chloroquinolin-3-yl) methoxy) benzaldehyde (3.4 mmol) (**4a**), 2-thiazolidinedione (3.4 mmol) (**5**) and L-proline (50 mole %) was heated in PEG-400 (10 g) at 60 °C. The progress of the reaction was monitored by thin layer chromatography. After heating the reaction mass for 1.5 h, it was allowed to cool to rt. Then ethanol (50 mL) was added to it and whole reaction mass was stirred and then filtered. The solid appeared was filtered, washed with ethanol and dried. The crude was crystallized using DMF-Ethanol. The collected filtrate was subjected for vacuum distillation for removal of ethanol and to recover PEG-400 as well as L-proline. The recovered mass of PEG-400 and L-proline was reused for same reaction sequence. Similarly the other compounds, (**6b-h**) of the series were synthesized.

(*Z*)-5-[4-(2-Chloroquinolin-3-yl) methoxy]benzylidine-thiazolidine-2,4-diones (6a): Yellow solid, mp 211-212 °C, Yield: 87%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.53 (br s, 1H, NH, exchangeable with D_2O, 2,4-TZD), 8.63 (s, 1H, quinoline ArH), 8.10 (d, 1H, *J* = 7.8 Hz, quinoline ArH), 8.01 (d, 1H, *J* = 8.40 Hz, quinoline ArH), 7.85 (m, 1H, quinoline ArH), 7.69 (m, 1H, quinoline ArH), 7.75 (s, 1H, olefenic proton), 7.62 (d, 2H, *J* = 8.70 Hz, ArH), 7.29 (d, 2H, *J* = 8.7 Hz, ArH), 5.39 (s, 2H, -OCH_2). ^{13}CNMR (75 MHz, DMSO, δppm): 168.10, 166.13, 159.55, 157.20, 149.04, 146.56, 138.58, 132.07, 131.10 (2C), 128.15 (2C), 127.59, 126.80 (2C), 126.30 (2C), 121.10, 115.75, 66.80.

DART-MS (ESI^+, *m/z*): 397 (M^+), 399 (M^++2).

(*Z*)-5-[4-(2-Chloro-8-methylquinolin-3-yl) methoxy]-benzylidinethiazolidine-2,4-diones (6b): Pale yellow solid, mp 219-220 °C, Yield: 85%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.57 (br s, 1H, NH, exchangeable with D_2O, 2,4-TZD), 8.59 (s, 1H, quinoline ArH). 7.93 (m, 1H, quinoline ArH), 7.78 (s, 1H, olefenic proton), 7.68 (m, 1H, quinoline ArH), 7.62 (m, 1H, quinoline ArH), 7.53 (m, 2H, ArH), 7.26 (d, 2H, *J* = 8.7Hz, ArH), 5.39 (s, 2H, -OCH_2), 2.86 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO, δppm): 167.27, 166.95, 159.33, 155.45, 145.41, 138.38, 135.09, 131.51, 131.07, 130.48, 127.59, 126.84 (2C), 126.54, 126.09 (2C), 125.47 (2C), 115.54, 66.67, 16.65. Anal. Calcd. For $C_{21}H_{15}ClN_2O_3S$: C, 61.39; H, 3.68; N, 6.82; S, 7.80. Found: C, 60.59; H, 3.64; N, 6.56; S, 7.53. DART-MS (ESI^+, *m/z*): 411 (M^+), 413 (M^++2).

(*Z*)-5-[4-(2-Chloro-7-methylquinolin-3-yl) methoxy]-benzylidinethiazolidine-2,4-diones (6c): Pale yellow solid, mp 217-218 °C, Yield: 84%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.53 (br s, 1H, NH, exchangeable with D_2O, 2,4-TZD), 8.57 (s, 1H, quinoline ArH), 7.98 (m, 1H, quinoline ArH), 7.78 (d, 1H, *J* = 8.43 Hz, quinoline ArH), 7.76 (d, 1H, *J* = 8.43 Hz, quinoline ArH), 7.61 (d, 2H, *J* = 8.7 Hz, ArH), 7.54 (s, 1H, olefenic proton), 7.27 (d, 2H, *J* = 8.7 Hz, ArH), 5.36 (s, 2H, -OCH_2), 2.53 (s, 3H, CH_3). DART-MS (ESI^+, *m/z*): 411 (M^+), 413 (M^++2).

(*Z*)-5-[4-(2-Chloro-6-methylquinolin-3-yl) methoxy]-benzylidinethiazolidine-2,4-diones (6d): Pale yellow solid, mp 230-231 °C, Yield: 85%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.51 (br s, 1H, NH, exchangeable with D_2O, 2,4-TZD), 8.53 (s, 1H, quinoline ArH), 7.95 (d, 1H, *J* = 8.10 Hz, quinoline ArH), 7.67 (s, 1H, quinoline ArH), 7.65 (d, 1H, *J* = 8.14 Hz, quinoline ArH), 7.59 (m, 2H, *J* = 8.40 Hz, ArH), 7.30 (d, 2H, *J* = 8.80 Hz, ArH), 7.58 (s, 1H, olefenic proton), 5.43 (s, 2H, -OCH_2), 2.56 (s, 3H, CH_3). DART-MS (ESI^+, *m/z*): 411 (M^+), 413 (M^++2).

(*Z*)-5-[4-(2-Chloro-7-methoxyquinolin-3-yl) methoxy]-benzylidinethiazolidine-2,4-diones (6e): Brown solid, mp 219-220 °C, Yield: 86%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.53 (br s, 1H, NH, exchangeable with D_2O, 2,4-TZD), 8.47 (s, 1H, quinoline ArH), 7.95 (s, 1H, quinoline ArH), 7.83 (d, 1H, *J* = 8.37 Hz, quinoline ArH), 7.73 (d, 1H, *J* = 8.43 Hz, quinoline ArH), 7.48 (d, 2H, *J* = 9.19 Hz, ArH), 7.56 (s, 1H, olefenic proton), 7.24 (d, 2H, *J* = 8.53 Hz, ArH), 5.37 (s, 2H, -OCH_2), 3.87 (s, 3H, OCH_3). DART-MS (ESI^+, *m/z*): 427 (M^+), 429 (M^++2).

(*Z*)-5-[4-(2-Chloro-6-methoxyquinolin-3-yl) methoxy]-benzylidinethiazolidine-2,4-diones (6f): Brown solid, mp 242-243 °C, Yield: 85%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.51 (br s, 1H, NH, exchangeable with D_2O, 2,4-TZD), 8.48 (s, 1H, quinoline ArH), 7.90 (d, 1H, *J* = 8.72 Hz, quinoline ArH), 7.75 (s, 1H, quinoline ArH), 7.62 (d, 1H, *J* = 8.72 Hz, quinoline ArH), 7.55 (s, 1H, olefenic proton), 7.48 (d, 2H, *J* = 9.16 Hz, ArH), 7.27 (d, 2H, *J* = 8.72 Hz, ArH), 7.24 (d, 2H, *J* = 8.53 Hz, ArH), 5.37 (s, 2H, -OCH_2), 3.89 (s, 3H, OCH_3). DART-MS (ESI^+, *m/z*): 427 (M^+), 429 (M^++2).

(*Z*)-5-[4-(2-Chloro-6-ethoxyquinolin-3-yl) methoxy]-benzylidinethiazolidine-2,4-diones (6g): Pale yellow solid, mp 238-239 °C, Yield: 83%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.49 (br s, 1H, NH, exchangeable with D_2O, 2,4-TZD), 8.46 (s, 1H, quinoline ArH), 7.92 (d, 1H, *J* = 8.30 Hz, quinoline ArH), 7.70 (s, 1H, quinoline ArH), 7.60 (d, 1H, *J* = 6.50 Hz, quinoline ArH), 7.46 (d, 2H, *J* = 6.51 Hz, ArH), 7.43 (s, 1H, olefenic proton), 7.26 (d, 2H, *J* = 6.51 Hz, ArH), 5.35 (s, 2H, -OCH_2), 4.14 (q, 2H, OCH_2CH_3), 1.39 (t, 3H,

OCH_2CH_3). DART-MS (ESI^+, *m/z*): 441 (M^+), 443 (M^++2).

(*Z*)-5-[4-(2,7-dichloroquinolin-3-yl) methoxy]benzyl-idinethiazolidine-2,4-diones (6h): White solid, mp 215-216 °C, Yield: 86%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.58 (br s, 1H, NH, exchangeable with D_2O, 2,4-TZD), 8.54 (s, 1H, quinoline ArH), 8.51 (s, 1H, quinoline ArH), 7.99 (d, 1H, *J* = 8.30 Hz, quinoline ArH), 7.68 (d, 1H, *J* = 8.43 Hz, quinoline ArH), 7.59 (d, 2H, *J* = 8.1 Hz, ArH), 7.58 (s, 1H, olefenic proton), 7.31 (d, 2H, *J* = 8.80 Hz, ArH), 5.75 (s, 2H, -OCH_2). DART-MS (ESI^+, *m/z*): 431 (M^+), 433 (M^++2), 435 (M^++4).

Experimental Procedure for the Synthesis of 3-(Hydroxy methyl)-2-chloroquinoline (2a). To the solution of 2-chloro-3-formyl quinoline (10 g, 52 mmol) (**1a**) in methanol (100 mL), $NaBH_4$ (1.98 g, 52 mmol) was added in portions. After the complete addition of $NaBH_4$ the mass was stirred at rt. The progress of the reaction was monitored by thin layer chromatography. After 30 min. of stirring the solvent was removed from the reaction mass under vacuum and the residue was added to ice cold water. The obtained solid was filtered, washed with water and dried. The purity of the product (**2a**) was confirmed by thin layer chromatography. It was used for the further reaction without any purification.

Similarly the other compounds, (**2b-h**) were synthesized by following the above procedure.

3-(Hydroxy methyl)-2-chloroquinoline (2a): White Solid, mp 148-149 °C, Yield: 87%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.29 (s, 1H, quinoline), 8.04 (d, 1H, *J* = 8.4 Hz, Ar-H quinoline), 7.84 (d, 1H, *J* = 6.0 Hz, quinoline Ar-H), 7.76 (t, 1H, *J* = 6.0 Hz, quinoline Ar-H), 7.55 (t, 1H, *J* = 9.0 Hz, quinoline Ar-H), 3.49 (s, 1H, OH, exchangeable with D_2O), 2.08 (s, 2H, CH_2) ppm. DART-MS (ESI^+, *m/z*): 194 (M^+), 196 (M^++2).

3-(Hydroxy methyl)-2-chloro-8-methylquinoline (2b): White Solid, mp 137-138 °C, Yield: 84%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.22 (s, 1H, quinoline), 7.66 (d, 2H, *J* = 6.0 Hz, quinoline Ar-H), 7.55 (t, 1H, *J* = 6.0 Hz, quinoline Ar-H), 7.45 (t, 1H, *J* = 6.0 Hz, quinoline Ar-H), 4.91 (s, 2H, CH_2), 3.49 (s, 1H, OH, exchangeable with D_2O), 2.76 (s, 3H, CH_3) ppm. DART-MS (ESI^+, *m/z*): 208 (M^+), 210 (M^++2).

3-(Hydroxy methyl)-2-chloro-7-methylquinoline (2c): White Solid, mp 144-145 °C, Yield: 87%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.15 (s, 1H, quinoline Ar-H), 7.8 (d, 1H, *J* = 8.3 Hz, quinoline Ar-H), 7.58 (s, 1H, quinoline Ar-H), 7.41(d, 1H, *J* = 8.1Hz, quinoline Ar-H), 4.92 (s, 2H, CH_2), 3.48 (s, 1H, OH, exchangeable with D_2O), 2.76 (s, 3H, CH_3) ppm. DART-MS (ESI^+, *m/z*): 208 (M^+), 210 (M^++2).

3-(Hydroxy methyl)-2-chloro-6-methylquinoline (2d): White Solid, mp 124-125 °C, Yield: 86%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.10 (s, 1H, quinoline Ar-H), 7.60 (d, 1H, *J* = 7.50 Hz, quinoline Ar-H), 7.58 (s, 1H, quinoline Ar-H), 7.40 (d, 1H, *J* = 7.30 Hz, quinoline Ar-H), 4.93(s, 2H, CH_2), 3.51(s, 1H, OH, exchangeable with D_2O), 2.77 (s, 3H, CH_3) ppm. DART-MS (ESI^+, *m/z*): 208 (M^+), 210 (M^++2).

3-(Hydroxy methyl)-2-chloro-7-methoxyquinoline (2e): White Solid, mp 197-198 °C, Yield: 85%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.01 (s, 1H, quinoline Ar-H), 7.26 (d, 1H, *J* = 8.50 Hz, quinoline Ar-H), 7.19 (d, 1H, *J* = 7.0 Hz, quinoline Ar-H), 7.02 (s, 1H, quinoline Ar-H), 5.03 (s, 2H, CH_2), 3.46 (s, 1H, OH, exchangeable with D_2O). GCMS (ESI^+, *m/z*): 224 (M^+), 226 (M^++2).

3-(Hydroxy methyl)-2-chloro-6-methoxyquinoline (2f): White Solid, mp 145-146 °C, Yield: 87%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.80 (s, 1H, quinoline Ar-H), 7.25 (d, 1H, *J* = 8.50 Hz, quinoline Ar-H), 7.20 (d, 1H, *J* = 7.0 Hz, quinoline Ar-H), 7.03 (s, 1H, quinoline Ar-H), 4.80 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.47 (s, 1H, OH, exchangeable with D_2O) ppm. GCMS (ESI^+, *m/z*): 224 (M^+), 226 (M^++2).

3-(Hydroxy methyl)-2-chloro-6-ethoxyquinoline (2g): White Solid, mp 121-123 °C, Yield: 86%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.74 (s, 1H, quinoline Ar-H), 7.42 (s, 1H, quinoline Ar-H), 7.26 (d, 1H, *J* = 7.50 Hz, quinoline Ar-H), 7.20 (d, 1H, *J* = 7.20 Hz, quinoline Ar-H), 4.85 (s, 2H, CH_2), 4.11 (m, 2H, -OCH_2CH_3), 3.70 (s, 1H, OH, exchangeable with D_2O), 1.76 (t, 3H, *J* = 7.10 Hz, -OCH_2CH_3)ppm. GCMS (ESI^+, *m/z*): 238 (M^+), 240 (M^++2).

3-(Hydroxy methyl)-2,7-dichloroquinoline (2h): White solid, mp 105-106 °C, Yield: 88%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.5 (s, 1H, quinoline Ar-H), 8.3 (s, 1H, quinoline Ar-H), 7.80 (d, 1H, *J* = 8.10 Hz), 7.6 (d, 1H, *J* = 7.60 Hz, quinoline Ar-H), 5.10 (s, 2H, CH_2), 3.80 (s, 1H, OH, exchangeable with D_2O) ppm. GCMS (ESI^+, *m/z*): 228 (M^+), 230 (M^++2), 232 (M^++4).

Experimental Procedure for the Synthesis of 3-(Tosyloxy methyl)-2-chloroquinoline (3a). (2-Chloroquinolin-3-yl) methanol (7.0 g, 36 mmol) (**2a**) and triethyl amine (5.4 g, 51 mmol) were dissolved in DCM (100 mL) and the solution was stirred for 30 min. To this stirred solution p-toluene sulphonyl chloride (7.6 g, 39 mmol) was added in portions at 0 °C. The progress of the reaction was monitored by thin layer chromatography. After 6 h of stirring, the solvent from the reaction mass was removed under vacuum. The residue was then poured in ice cold water. The solid was obtained filtered, washed by water and dried. After confirming purity on TLC the dried product was used for the further reaction without any purification.

Similarly the other compounds, (**3b-h**) of the series were synthesized by following the above same procedure.

3-(Tosyloxy methyl)-2-chloroquinoline (3a): White Solid, mp 98-99 °C, Yield: 82%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.29 (s, 1H, quinoline), 8.03 (d, 1H, *J* = 6.0 Hz, quinoline Ar-H), 8.03 (d, 1H, *J* = 9.0 Hz, quinoline Ar-H),7.90 (d, 2H, *J* = 7.50 Hz, Ar-H), 7.85 (d, 1H, *J* = 6.0 Hz, quinoline Ar-H), 7.77 (t, 1H, *J* = 6.0 Hz, quinoline Ar-H), 7.75 (d, 2H, *J* = 7.50 Hz, Ar-H), 7.58 (t, 1H, *J* = 9.0 Hz, quinoline Ar-H), 4.85 (s, 2H, CH_2), 1.56 (s, 3H, CH_3) ppm. DART-MS (ESI^+, *m/z*): 348 (M^+), 350 (M^++2).

3-(Tosyloxy methyl)-2-chloro-8-methylquinoline (3b): White Solid, mp 78-79 °C, Yield: 76%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.23 (s, 1H, quinoline Ar-H), 7.80 (d, 2H, *J* = 7.1Hz, Ar-H), 7.67 (d, 1H, *J* = 9.0 Hz, quinoline Ar-H), 7.60 (d, 2H, *J* = 7.60 Hz, Ar-H), 7.59 (d, 1H, *J* = 6.0 Hz, quinoline Ar-H), 7.48 (t, 1H, *J* = 12.0 Hz, quinoline Ar-H), 4.92 (s, 2H, CH_2), 2.77 (s, 3H, CH_3) ppm. DART-MS (ESI^+,

m/z): 362 (M^+), 364 (M^++2).

3-(Tosyloxy methyl)-2-chloro-7-methylquinoline (3c): White Solid, mp 121-122 °C, Yield: 75%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.15 (s, 1H, quinoline Ar-H), 7.81 (d, 2H, *J* = 7.72 Hz, Ar-H), 7.70 (d, 1H, *J* = 8.1 Hz, quinoline Ar-H), 7.51 (d, 1H, *J* = 7.90 Hz, quinoline Ar-H), 7.67 (s, 1H, quinoline Ar-H), 7.51 (d, 1H, *J* = 7.90 Hz, quinoline Ar-H), 4.92 (s, 2H, CH_2), 2.76 (s, 3H, CH_3), 2.61 (s, 3H, CH_3) ppm. DART-MS (ESI^+, *m/z*): 362 (M^+), 364 (M^++2).

3-(Tosyloxy methyl)-2-chloro-6-methylquinoline (3d): White Solid, mp 101-102 °C, Yield: 87%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.11 (s, 1H, quinoline Ar-H), 7.80 (d, 2 H, *J* = 7.70 Hz, Ar-H), 7.69 (d, 1H, *J* = 7.90 Hz, quinoline Ar-H), 7.55 (s, 1H, quinoline Ar-H), 7.51 (d, 2H, *J* = 7.58 Hz, Ar-H), 7.41 (d, 1H, *J* = 7.80 Hz, quinoline Ar-H), 4.94 (s, 2H, CH_2), 2.77 (s, 3H, CH_3), 2.60 (s, 3H, CH_3) ppm. DART-MS (ESI^+, *m/z*): 362 (M^+), 364 (M^++2).

3-(Tosyloxy methyl)-2-chloro-7-methoxylquinoline (3e): White Solid, mp 124-125 °C, Yield: 83%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.80 (s, 1H, quinoline Ar-H), 7.73 (d, 2H, *J* = 7.65 Hz, Ar-H), 7.50 (d, 2H, *J* = 7.65 Hz, Ar-H), 7.24 (d, 1H, *J* = 8.40 Hz, quinoline Ar-H), 7.19 (d, 1H, *J* = 7.60 Hz, quinoline Ar-H), 7.03 (s, 1H, quinoline Ar-H), 4.60 (s, 2H, -CH_2-), 3.76 (s, 3H, OCH_3), 2.52 (s, 3H, CH_3) ppm. GCMS (MS^+, *m/z*): 378 (M^+), 380 (M^++2).

3-(Tosyloxy methyl)-2-chloro-6-methoxylquinoline (3f): White Solid, mp 131-132 °C, Yield: 84%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.81 (s, 1H, quinoline Ar-H), 7.7 (d, 2H, *J* = 7.65 Hz, Ar-H), 7.40 (d, 2H, *J* = 7.65 Hz, Ar-H), 7.24 (d, 1H, *J* = 8.5 Hz, quinoline Ar-H), 7.21 (d, 1H, *J* = 7.0 Hz, quinoline Ar-H), 7.01 (s, 1H, quinoline Ar-H), 4.70 (s, 2H, -CH_2-), 3.80 (s, 3H, OCH_3), 2.53 (s, 3H, CH_3) ppm. GCMS (ESI^+, *m/z*): 378 (M^+), 380 (M^++2).

3-(Tosyloxy methyl)-2-chloro-6-ethoxylquinoline (3g): White Solid, mp 110-111 °C, Yield: 83%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.77 (s, 1H, quinoline Ar-H), 7.60 (d, 2H, *J* = 7.68 Hz, Ar-H), 7.41 (s, 1H, quinoline Ar-H), 7.30 (d, 2H, *J* = 7.40 Hz, Ar-H), 7.25 (d, 1H, *J* = 7.40 Hz, quinoline Ar-H), 7.19 (d, 1H, *J* = 7.60 Hz, quinoline Ar-H), 4.80 (s, 2H, -CH_2-), 4.10 (q, 2H, *J* = 7.60 Hz, CH_2CH_3), 2.53 (s, 3H, CH_3), 1.37 (t, 3H, *J* = 7.11 Hz, CH_2CH_3) ppm. GCMS (ESI^+, *m/z*): 392 (M^+), 394 (M^++2).

3-(Tosyloxy methyl)-2,7-dichloroquinoline (3h): White Solid, mp 97-98 °C, Yield: 80%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.40 (s, 1H, quinoline Ar-H), 8.1 (s, 1H, quinoline Ar-H), 7.90 (d, 2H, *J* = 8.50 Hz, Ar-H), 7.70 (d, 1H, *J* = 8.10 Hz, quinoline Ar-H), 7.50 (d, 1H, *J* = 7.90 Hz, quinoline Ar-H), 7.20 (d, 2H, *J* = 8.0 Hz, quinoline Ar-H), 4.91 (s, 2H, CH_2), 2.61 (s, 3H, CH_3) ppm. GCMS (ESI^+, *m/z*): 382 (M^+), 384 (M^++2), 386 (M^++4).

Experimental Procedure for the Synthesis of 4-((2-chloroquinolin-3-yl) methoxy) Benzaldehyde (4a): A mixture of 4-hydroxybenzaldehyde (1.82 g, 15 mmol) and potassium carbonate (2.71 g, 20 mmol) was stirred in DMF (60 mL) for 20 min. at 80 °C. To this then (2-chloroquinolin-3-yl) methyl 4-methylbenzenesulfonate (**3a**) (5 g, 14 mmol) was added and the content was further stirred for 3 h at 80 °C. The progress of the reaction was monitored by thin layer chromatography. After 3 h of heating at 80 °C, the reaction mass was allowed to cool at rt and poured on crushed ice. The obtained solid was filtered, washed with water and crystallized using ethanol. Similarly the other compounds, (**4b-h**) of the series were synthesized by following the same synthetic procedure.

4-((2-Chloroquinolin-3-yl) methoxy) benzaldehydes (4a): White Solid, mp 118-119 °C, Yield: 83%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 9.90 (s, 1H, CHO), 8.64 (s, 1H, quinoline Ar-H), 8.08 (d, 1H, *J* = 6.0 Hz, quinoline Ar-H), 7.99 (d, 2H, *J* = 9.0 Hz, Ar-H), 7.92 (d, 1H, *J* = 9.0 Hz, quinoline Ar-H), 7.85 (t, 1H, *J* = 6.0 Hz, quinoline Ar-H), 7.69 (t, 1H, *J* = 9.0 Hz, quinoline Ar-H), 7.32 (t, 1H, *J* = 9.0 Hz, quinoline Ar-H), 5.43 (s, 2H, CH_2)ppm. DART-MS (ESI^+, *m/z*): 298 (M^+), 300 (M^++2).

4-((2-Chloro-8-methylquinolin-3-yl) methoxy) benzaldehyde (4b): White Solid, mp 135-136 °C, Yield: 87%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 9.89 (s, 1H, CHO), 8.59 (s, 1H, quinoline Ar-H), 7.90 (t, 2H, *J* = 9.0 Hz, quinoline Ar-H), 7.69 (d, 2H, *J* = 6.0 Hz, Ar-H), 7.56 (t, 1H, *J* = 6.0 Hz, quinoline Ar-H), 7.32 (d, 2H, *J* = 9.0 Hz, Ar-H), 5.42 (s, 2H, CH_2), 2.67 (s, 3H, CH_3)ppm. DART-MS (ESI^+, *m/z*): 312 (M^+), 314 (M^++2).

4-((2-Chloro-7-methylquinolin-3-yl)methoxy)benzaldehyde (4c): White Solid, mp 138-139 °C, Yield: 82%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 9.83 (s, 1H, CHO), 8.61 (s, 1H, quinoline Ar-H), 7.92 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.63 (d, 1H, *J* = 8.0 Hz, quinoline Ar-H), 7.51 (d, 1H, *J* = 7.9 Hz, quinoline Ar-H), 7.11 (d, 2H, *J* = 6.8 Hz, Ar-H), 5.13 (s, 2H, CH_2), 2.77 (s, 3H, CH_3) ppm. DART-MS (ESI^+, *m/z*): 312 (M^+), 314 (M^++2).

4-((2-Chloro-6-methylquinolin-3-yl)methoxy)benzaldehyde (4d): White Solid, mp 140-141 °C, Yield: 87%. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 9.85 (s, 1H, CHO), 8.30 (s, 1H, quinoline Ar-H), 7.90 (d, 2H, *J* = 8.60 Hz, Ar-H), 7.60 (d, 1H, *J* = 8.10Hz, quinoline Ar-H), 7.60 (s, 1H, quinoline Ar-H), 7.48 (d, 1H, *J* = 7.80 Hz, quinoline Ar-H), 7.20 (d, 2H, *J* = 7.20 Hz, Ar-H), 5.10 (s, 2H, CH_2), 2.76 (s, 3H, CH_3) ppm. DART-MS (ESI^+, *m/z*): 312 (M^+), 314(M^++2).

4-((2-Chloro-7-methoxyquinolin-3-yl)methoxy)benzaldehyde (4e): White Solid, mp 128-129 °C, Yield: 86%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.89 (s, 1H, CHO), 7.81 (s, 1H, quinoline Ar-H), 7.77 (d, 2H, *J* = 8.20 Hz, Ar-H), 7.28 (d, 1H, *J* = 8.60 Hz, quinoline Ar-H), 7.23 (d, 1H, *J* = 8.20 Hz, quinoline Ar-H), 7.12 (d, 2H, *J* = 6.9 Hz, Ar-H), 5.17 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3) ppm. GCMS (ESI^+, *m/z*): 328 (M^+), 330 (M^++2).

4-((2-Chloro-6-methoxyquinolin-3-yl)methoxy)benzaldehyde (4f): White Solid, mp 126-127 °C, Yield 83%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.88 (s, 1H, CHO), 7.80 (s, 1H, quinoline Ar-H), 7.75 (d, 2H, *J* = 8.20 Hz, Ar-H), 7.26 (d, 1H, *J* = 8.50 Hz, quinoline Ar-H), 7.22 (d, 1H, *J* = 7.10 Hz, quinoline Ar-H), 7.10 (d, 2H, *J* = 6.80 Hz, Ar-H), 7.02 (s, 1H, quinoline Ar-H), 5.14 (s, 2H, -CH_2O), 3.70 (s, 3H, OCH_3) ppm. GCMS (ESI^+, *m/z*): 328 (M^+), 330 (M^++2).

4-((2-Chloro-6-ethoxyquinolin-3-yl)methoxy)benzaldehyde

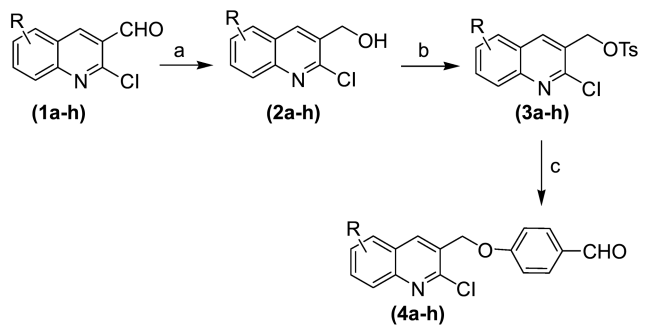
(4g): White Solid, mp 120-121 °C, Yield: 84%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.83 (s, 1H, CHO), 7.80 (s, 1H, quinoline Ar-H), 7.70 (d, 2H, *J* = 7.80 Hz, Ar-H), 7.42 (s, 1H, quinoline Ar-H), 7.28 (d, 1H, *J* = 7.50 Hz, quinoline Ar-H), 7.20 (d, 1H, *J* = 7.60 Hz, quinoline Ar-H), 7.15 (d, 2H, *J* = 7.10 Hz, Ar-H), 5.10 (s, 2H, -CH_2O), 4.10 (m, 2H, OCH_2CH_3), 1.37 (t, 3H, *J* = 7.10 Hz, OCH_2CH_3) ppm. GCMS (ESI^+, *m/z*): 342 (M^+), 344 (M^++2).

4-((2,7-Dichloroquinolin-3-yl)methoxy)benzaldehyde (4h): White Solid, mp 132-133 °C, Yield: 81%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.93 (s, 1H, CHO), 8.50 (s, 1H, quinoline Ar-H), 7.93 (d, 2H, *J* = 8.40 Hz, Ar-H), 7.80 (d, 1H, *J* = 8.10 Hz, quinoline Ar-H), 7.50 (d, 1H, *J* = 7.60 Hz, quinoline Ar-H), 7.30 (d, 2H, *J* = 8.10 Hz, Ar-H), 5.05 (s, 2H, CH_2) ppm. GCMS (ESI^+, *m/z*): 332 (M^+), 334 (M^++2), 336 (M^++4).

Results and Discussion

4-((2-Chloroquinolin-3-yl) methoxy) benzaldehydes, (**4a-h**) the required precursors were freshly prepared by following the reaction sequences presented in Scheme 1 using known 2-chloro-3-formyl quinolines, (**1a-h**).[11] The compounds, (**1a-h**) were reduced[18] by sodium borohydride and obtained 3-(hydroxy methyl)-2-chloroquinolines, (**2a-h**). The methanols when treated with *p*-toluene sulphonyl chloride in presence of triethylamine gave tosylated products, 3-(tosyloxy methyl)-2-chloroquinolines, (**3a-h**). The sulphonates, (**3a-h**) on the condensation with *p*-hydroxy benzaldehyde in DMF in presence of potassium carbonate yielded the new precursors, 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes, (**4a-h**) with good to moderate yields (Scheme 1).

To select the appropriate catalyst initially the condensation of 4-((2-chloroquinolin-3-yl) methoxy) benzaldehyde (**4a**) and 2,4-thiazolidinedione **5** was run in various solvents and catalysts. The above model reaction was attempted in piperidine in toluene and pyrrolidine in toluene at refluxed condition and noticed that the condensation did not take place even at reflux for 1.5 h. To choose the appropriate catalyst and medium, we run the model reaction by varying the above factors and the observations are recorded in the Table 1. Here we noticed that condensation gave better results if carried in PEG-400 as safer medium and using



Scheme 1. Reagents and conditions: (a) $NaBH_4$, CH_3OH, rt, 30 min; (b) Triethyl amine, *p*-TsCl, DCM, rt 5-6 h; (c) P-OH-benzaldehyde, K_2CO_3, DMF, 80 °C, 3 h.

Table 1. Optimization of catalysts for the synthesis of **6a**

Entry	Catalysts	Time (h)	Isolated Yield (%)
1	None	1.5	No reaction
2	Piperidine in Toluene[a]	1.5	No reaction
3	Pyrrolidine and Toluene[a]	1.5	No reaction
4	Sodium acetate and acetic acid[a]	1.5	43
5	PEG-400[b]	1.5	No reaction
6	PEG-400 and triethyl amine[b]	1.5	53
7	PEG-400 and L-Proline[c]	1.5	87

[a]Reactions carried at the refluxed temperature of the respective solvents. [b]Reaction carried at 130 °C. [c]Reaction carried at 60 °C.

Table 2. Optimization of amount of L-proline

Entry	Amount (mole %)	Reaction Time (h)[a]	Yield (%)[b]
1	10	1.5	No reaction
2	20	1.5	53
3	30	1.5	59
4	40	1.5	68
5	50	1.5	87
6	60	1.5	87-88

[a]Reaction carried at 60 °C. [b]Isolated yield of (**6a**).

Table 3. Recovery and Reusability of L-Proline and PEG-400

Batch[a]	Yield (%)[b]
Fresh	87
I	85
II	84
III	83

[a]Reaction carried at 60 °C. [b]Isolated yield of (**6a**).

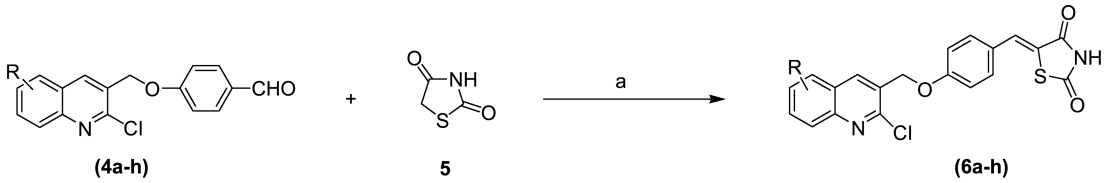
L-proline as organocatalyst. From these observations it was concluded that this condensation has been found to be practicable if carried in PEG-400 at 60 °C using L-proline as organobase catalyst.

To investigate the amount of L-proline required for the formation of (**6a**), the model reaction was attempted by

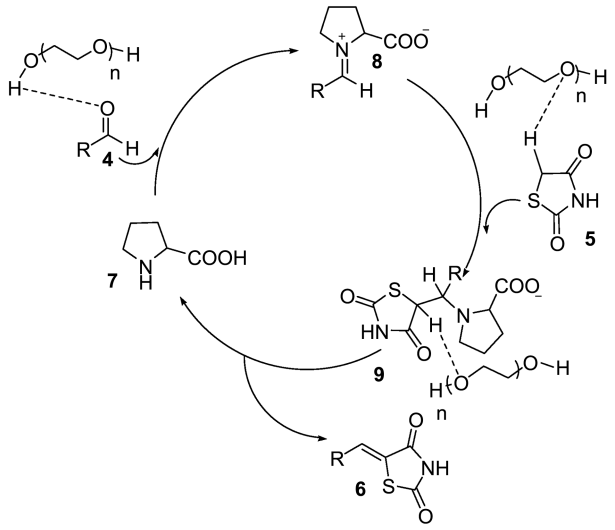
Table 4. Synthesis of (*Z*)-5-[4-(2-chloroquinolin-3-yl) methoxy]-benzylidinethiazolidine-2,4-diones derivative using Oganocatalyst and PEG-400

Entry	R	Products[a]	Yield (%)[b]	mp (°C)
1	H	**6a**	87	211-212
2	8-CH_3	**6b**	85	219-220
3	7-CH_3	**6c**	84	217-218
4	6-CH_3	**6d**	85	230-231
5	7-O CH_3	**6e**	86	203-204
6	6-O CH_3	**6f**	85	224-225
7	6-O CH_2CH_3	**6g**	83	238-239
8	7-Cl	**6h**	86	215-216

[a]All products were characterized by ^{1}H-NMR and Mass spectral analyses. [b]Isolated yields of products.



Scheme 2. Reagents and conditions: (a) L-proline, PEG-400, 60 °C, 1.5 h.



Scheme 3

varying the amount of L-proline in the range of 10-60 mole %. It was observed that with increase in concentration of L-proline the yield of (**6a**) has been increased. The optimum concentration of L-proline was found to be 50 mole %. When the amount of L-proline used was more than 50 mole % there was no any substantial change in the yield of the product, (**6a**) (Table 2).

The developed synthetic strategy has been found to be economic as L-proline and PEG-400 are recoverable and can be recycled to run the same condensations (Table 3).

With all the above optimized conditions in hand, we continued to apply the approach to condense 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes (**4a-h**) and 2,4-thiazolidinedione (**5**) using L-proline in greener reaction medium, PEG-400 in presence of L-proline and obtained (*Z*)-5-[4-(2-chloroquinolin-3-yl) methoxy]benzylidinethiazolidine-2,4-diones (**6a-h**) with excellent yields (Table 4) (Scheme 2). It is noteworthy to mention that the methodology worked well to both electron donating and withdrawing substituent on 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes (**4a-h**).

The plausible mechanism has been depicted in Scheme 3 for the condensation of 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes (**4a-h**) and 2,4-thiazolidinedione **5**, carried in PEG-400 and in the presence of organocatalyst, L-proline leading to (*Z*)-5-[4-(2-chloroquinolin-3-yl) methoxy]benzylidinethiazolidine-2,4-diones (**6a-h**).

Conclusion

We have synthesized new (*Z*)-5-[4-(2-chloroquinolin-3-yl) methoxy]benzylidinethiazolidine-2,4-diones. The fascinating scope of this synthetic strategy is that the products and intermediates obtained were from readily available materials and are non ambiguous. We have used naturally occurring organocatalyst, L-proline and environmental benign reaction media PEG-400 for the Knoevenagel condensation of 4-((2-chloroquinolin-3-yl) methoxy) benzaldehydes, (**4a-h**) and 2,4-thiazolidinedione (**5**) leading to new (*Z*)-5-[4-(2-chloroquinolin-3-yl) methoxy]benzylidinethiazolidine-2,4-diones. This protocol circumvents the problems associated with the toxic and hazardous catalysts and organic solvents.

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References

1. (a) Oguchi, M.; Wada, K.; Honma, H.; Tanaka, A.; Taneko, T.; Sakakibara, S.; Ohsumi, J.; Serizawa, N.; Fujiwara, T.; Horikoshi, H.; Fujita, T. *J. Med. Chem.* **2000**, *43*, 3052. (b) Malamas, M. S.; Sredy, J.; Gunawan, I.; Mihan, B.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Flam, B. R. *J. Med. Chem.* **2000**, *43*, 995.
2. (a) Saltiel, A. R.; Olefsky, J. M. *Diabetes* **1996**, *45*, 1661. (b) Fujita, T.; Sugiyama, Y.; Taketomi, S.; Sohda, T.; Kawamatsu, Y.; Iwatsuka, H.; Suzuoka, Z. *Diabetes* **1983**, *32*, 804. (c) Chang, A. Y.; Wyse, B. M.; Gilchrist, B. J.; Peterson, T.; Diani, A. R. *Diabetes* **1983**, *32*, 830.
3. (a) Lehman, J. M.; Moore, L. B.; Smith Oliver, T. A.; William, O. W.; Willson, T. M.; Kliewer, S. A. *J. Biol. Chem.* **1995**, *270*, 12953. (b) Klirwer, S. A.; Lenhard, J. M.; Wilson, T. M. *Cell* **1995**, *83*, 813.
4. (a) Momose, Y.; Meguro, K.; Ikeda, H.; Hatanka, C.; Oi, S.; Sohda, T. *Chem. Pharm. Bull.* **1991**, *39*, 1440. (b) Cantello, B. C. C.; Cawthorne, M. A.; Haigh, D.; Hindley, R. M.; Smith, S. A.; Thurlby, P. L. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1181. (c) Momura, M.; Kinoshita, S.; Satoh, H.; Maeda, T.; Murakami, K.; Tsunodam, M.; Miyachi, H.; Awano, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 533. (d) Hong, W. L.; Joong, B. A.; Sung, K. K.; Soon, K. A.; Deok, C. H. *Org. Proc. Res. & Dev.* **2007**, *11*, 190. (e) Brag, B. L.; Vidya, B.; Bheema, P. R.; Gurram, R. M.; Nagahelli, M.; Kovvidi, N. R.; Pmaulapati, G. R.; Chakraborthy, R.; Reeba, K. V.; Ramanujam, R.; Rao, N. V.; Hemant, K. J.; Swaminathan, S. http://pubs.acs.org/doi/abs/10.1021/jm970444e *J. Med. Chem.* **1998**, *41*, 1619.
5. (a) Lesyk, R. B.; Zimenkovsky, B. S.; Troc'ko, N. *Ukrainica Bioorganica Acta.* **2004**, *1*, 29. (b) Lesyk, R. B.; Zimenkovsky, B. S. *Curr. Org. Chem.* **2004**, *8*, 1547.
6. (a) Mohareb, R. M.; Fleita, D. H. *Heteroatom Chem.* **2002**, *13*, 258. (b) Herrding, D. A.; Christmann, L. T.; Clark, T. J.; Holmes, D. J.; Rittenhouse, S. F.; Takata, D. T.; Venslavsky, J. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3771. (c) Bruno, G.; Costantino, L.;

Curinga, C.; Maccari, R.; Monforte, F.; Nicolo, F.; Ottana, R.; Vigoritac, M. G. *Bioorg. & Med. Chem*. **2002**, *10*, 1077. (d) Ali, A. M.; Saber, G. E.; Mahfouz, N. M.; El-Gendy, M. A.; Radwan, A. A.; Hamid, M. A. *Arch Pharm. Res.* **2007**, *30*, 1186. (e) Maccari, R.; Ottanà, R.; Ciurleo, R.; Rakowitz, D.; Matuszczak, B.; Laggner, C.; Langer, T. *Bioorg. & Med. Chem.* **2008**, *16*, 5840. (f) Luo, Y.; Ma, L.; Zheng, H.; Chen, L.; Li, R.; He, C.; Yang, S.; Ye, X.; Chen, Z.; Li, Z.; Gao, Y.; Han, J.; He, G.; Yang, L.; Wei, Y. *J. Med. Chem.* **2010**, *53*, 273.

7. Gubert, S.; Braojos, C.; Anglada, L.; Bolos, J.; Pllacin, C. *J. Heterocycl. Chem.* **1992**, *29*, 55.
8. Alhaider, A. A.; Adbekader, M. A.; Lien, E. J. *J. Med. Chem.* **1985**, *28*, 1394.
9. Cai, W.; Xu, D.; Yiyao, G. **1987**, *18*, 62. Chem Abstr 107, **1987**, 236651v.
10. Edmont, D.; Rocher, R.; Plisson, C.; Chenault, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1831.
11. (a) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J. Chem. Soc. Perkin Trans. 1* **1981**, 1520. (b) Bekhit, A. A.; El-Sayed, O. A.; Aboulmagd, E.; Park, J. Y. *Eur. J. Med. Chem.* **2004**, *39*, 249.
12. Gadekar, L. S.; Arbad, B. R.; Lande, M. K. *Org. Chem.: An Ind. J.* **2008**, *4*, 458.
13. Shelke, K. F.; Sapkal, S. B.; Kakade, G. K.; Sadaphal, S. A.; Shingate, B. B.; Shingare, M. S. *Green Chem. Lett. Rev.* **2010**, *3*, 17.
14. Bhattarai, B. R.; Kafle, B.; Hwang, J. S.; Khadka, D.; Lee, S. M.; Kang, J. S.; Hamd, S. W.; Han, I. O.; Park, H.; Cho, H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6161.
15. (a) Madhavan, G. R.; Chakrabarti, R. K.; Reddy, A.; Rajesh, B. M.; Balraju, V.; Rao, R. B.; Iqbal, J. *Bioor & Med. Chem*. **2006**, *14*, 584. (b) Madhavan, G. R.; Chakrabarti, R.; Kumar, S. K. B.; Misra, P.; Rao, N. V. S.; Balraju, M. V.; Kasiram, K.; Babu, R. K.; Suresh, J.; Lohray, B. B.; Lohray, V. B.; Iqbal, J.; Rajagopalan, R. *Euro. J. Med. Chem*. **2001**, *36*, 627.
16. Yoshitata, O.; Teruo, M.; Mishiko, N.; Motoyuki, J.; Norio, K. *Chem. Pharm. Bull.* **1992**, *40*, 907.
17. Liu, Z.; Huang, Y.; Zhang, W.; Ma, L.; Li, J.; Wang, X.; Li, J.; Shen, J. *J. Comb. Chem.* **2008**, *10*, 632.
18. Pokalwar, R. U.; Hangarge, R. V.; Kategaonkar, A. H.; Shingare, M. S. *Russian J. Org. Chem.* **2009**, *45*, 430.