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SYNTHESIS AND CHARACTERIZATION OF 3-(2-METHYLINDOLINE-1-Yl)-2- SUBSTITUTED PHENYLTHIAZOLIDIN-4- ONES USING THIOGLYCOLIC ACID

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ABSTRACT
Synthesize various 4-thiazolidinones appended with 2-methyl indoline as a core fragment. Thiazolidinone, a saturated form of thiazoles with carbonyl group on fourth carbon, has been considered as a moiety of choice as it possesses a broad spectrum of pharmacological activities against several targets. The main strategy of the reaction proceeds by the attack of mercapto acetic acid upon the C=N group, with the HS-CH_2-COOH adding to the carbon atom followed by capture of the proton by nitrogen and subsequent cyclization. During the reaction an uncyclized intermediate is formed in few cases. In many instances 4-Thiazolidinones can conveniently be prepared by refluxing the mixture of thioglycolic acid and the Schiff base in benzene, dry ether or ethanol.

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Key words: *Synthesis, 4-thiazolidinones, cyclization, mercapto acetic acid.*

INTRODUCTION

Thiazolidinone, a saturated form of thiazoles with carbonyl group on fourth carbon, has been considered as a moiety of choice as it possesses a broad spectrum of pharmacological activities against several targets. This array of biological response profile has attracted the attention of scientists' the world over to further investigate the potential of this organic motif. The referencing on this topic revealed that a lot of work has been done in this particular field in past.

4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4-position. Substituents in the 2, 3, and 5-positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position. Several protocols for the synthesis of 4-thiazolidinones are available in the literature [1-9]. Essentially they are three component reactions involving an amine, a carbonyl compound, and a mercapto-acid. The process can be either a one-pot three component condensation or a two-step

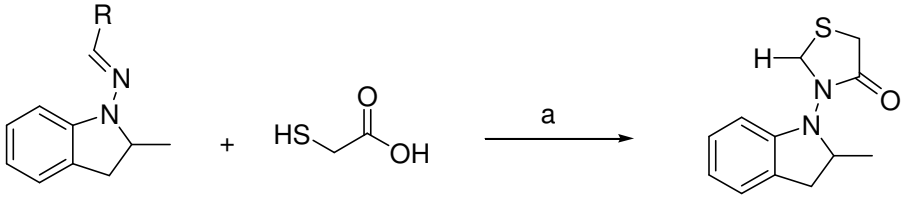
process [10-12]. An improved protocol has been reported wherein N, N-dicyclohexyl carbodiimide (DCC) or 2-(1H-benzotriazo-1-yl)-1, 1, 3, 3-tetramethyl uranium hexa-fluorophospate (HBTU) is used as a dehydrating agent to accelerate the intramolecular cyclization resulting in faster reaction and improved yields [13-14]. The DCC/HBTU-mediated protocol has the advantage of mild reaction conditions, a very short reaction time, and product formation in almost quantitative yields. More importantly, yields of the 4-thiazolidinones are independent of the nature of the reactants. This modification is compatible with a solid-phase combinatorial approach to generate a library of compounds.

One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures [15], with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry [16]. There are numerous biologically active molecules with five membered rings, containing two hetero atoms. Thiazolidine is an important scaffold known to be associated with several biological activities [17].

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 pellet method. Mass spectra were recorded on Shimadzu GCMS- QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer.

Synthetic Scheme



R = 1) benzene
2) 3-chloro benzene
3) 3-nitro benzene
4) 4-chloro benzene
5) 4-nitro benzene

Reagents & Conditions: a) Sulphuric acid, water

RESULTS AND DISCUSSION

The main deals with the 3-(2-methylindolin-1-yl) thiazolidin-4-one core structure. The importance of 2-Methylindoline-1-amine as a privileged structure as well as the biological significance of thiazolidinones. Previously, the thiazolidinone moiety was prepared by refluxing the Schiff base with the thioglycolic acid for longer time in presence of various different solvents as well as catalysts. In the recent years, many new synthetic methodologies haven been used such as synthesis using Ionic liquids, synthesis using better catalysts such as DCC and HBTU etc. and also using Microwave irradiation. The synthesis has been taken up using sulphuric acid over other methods owing to their advantages such as reduction in time, higher yields as well as hassle free work up procedures on one hand and on the other hand it is a small step forward in our endeavor towards the sustainable development through implementing the newer research work using eco-friendly processes.

The reaction proceeds by the attack of mercapto acetic acid upon the C=N group, with the HS-CH_2-COOH adding to the carbon atom followed by capture of the proton by nitrogen and subsequent cyclization. During the reaction an uncyclized intermediate is formed in few cases. In many instances 4-Thiazolidinones can conveniently be prepared by refluxing the mixture of thioglycolic acid and the Schiff base in benzene, dry ether or ethanol. The nucleophilic attack of the mercaptoacetic acid anion will take place on the carbon of azomethine which has got a positive character; while it is evident that the nitrogen has the negative character. Simultaneous removal of water that forms in the reaction helps in condensation and determination of the reaction time.

EXPERIMENTAL

General procedure

3-(2-Methylindolin-1-yl)-2-substituted phenyl thiazolidin-4-ones

N-substituted benzylidene-2-methylindoline-1-amine (1 mole), 2-mercaptoacetic acid (1 mole) and 1 mole of sulphuric acid was taken in a round bottom flask fixed with reflux condenser and heated the reaction mixture at 95^0C for 12 hours then adjusted pH 7 with sodium carbonate. The organic mass was extracted using ethyl acetate thrice. The combined organic extracts were then washed thrice with demineralized water to remove traces of acids from the reaction. Distilled u/vacuum completely then recrystallized in ethanol.

Preparation of 3-(2-methylindolin-1-yl)-2-phenyl thiazolidin-4-one (1).

Yield: 78%; M.P.- 178-180 ºC; IR (cm^{-1}): 1615 (Ring stretching for Indoline), 1414 (Ring stretching modes for thiazolidinone ring), 875-660 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2972-2935 (C-H asymmetric stretching for R-CH_3), 2855 (C-H symmetric stretching for R-CH_3), 1447 (C-H asymmetric bending for R-CH_3), 1382 (C-H symmetric bending for R-CH_3), 3080- 3000 (C-H stretching frequency for aromatic region), 1590 (C-C skeletal stretching of phenyl nucleus), 1238 (C-H in plane bending for phenyl ring), 710 (C-C out of plane bending for mono substituted benzene ring), 2925 (C-H stretching frequency for ketone), 1750 (C=O stretching frequency for ketone in 5 membered saturated ring), 1080-1025 (C-N stretching frequency for tertiary amine); MS: *m/z:* 310.11;

Preparation of 2-(3-chlorophenyl)-3-(2-methylindolin-1-yl) thiazolidin-4-one (2).

Yield: 74%; M.P.- 190-192 ºC; IR (cm^{-1}): 1600 (Ring stretching for Indoline), 1393 (Ring stretching modes for thiazolidinone ring), 860-640 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2945-2915 (C-H asymmetric stretching for R-CH_3), 2838 (C-H symmetric stretching for R-CH_3), 1430 (C-H asymmetric bending for R-CH_3), 1359 (C-H symmetric bending for R-CH_3), 3095-3005 (C-H stretching frequency for aromatic region), 1575 (C-C skeletal stretching of phenyl nucleus), 1216 (C-H in plane bending for phenyl ring), 705 (C-H out of plane bending for 1,3-Disubstituted benzene ring), 2905 (C-H stretching frequency for ketone), 1730 (C=O stretching frequency for ketone in 5 membered saturated ring), 1066-1007 (C-N stretching frequency for tertiary amine), 757 (C-Cl stretching frequency for mono chlorinated aromatic compounds); MS: *m/z:* 344.08

Preparation of 3-(2-methylindolin-1-yl)-2-(3-nitrophenyl) thiazolidin-4-one (3).

Yield: 75 %; M.P.- 174-176 ºC; IR (cm^{-1}): 1617 (Ring stretching for Indoline), 1409 (Ring stretching modes for thiazolidinone ring), 866-680 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2968-2931 (C-H asymmetric stretching for R-CH_3), 2852 (C-H symmetric stretching for R-CH_3), 1438 (C-H asymmetric bending for R-CH_3), 1373 (CH symmetric bending for R-CH_3), 3094-3015 (C-H stretching frequency for aromatic region), 1579 (C-C skeletal stretching of phenyl nucleus), 1223 (C-H in plane bending for phenyl ring), 717 (C-C out of plane bending for 1,3-Disubstituted benzene ring),

2921 (C-H stretching frequency for ketone), 1746 (C=O stretching frequency for ketone in 5 membered saturated ring), 1083-1021 (C-N

stretching frequency for tertiary amine), 1539-1527 (NO_2 asymmetric stretching frequency for aromatic Nitro group), 1308 (NO_2 symmetric stretching for aromatic NO_2 group); MS: *m/z:* 355.10

Preparation of 2-(4-chlorophenyl)-3-(2-methylindolin-1-yl) thiazolidin-4-one (4).

Yield: 80%; M.P.- 208-210 ºC; IR (cm^{-1}): 1603 (Ring stretching for Indoline), 1417 (Ring stretching modes for thiazolidinone ring), 873-657 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2975-2915 (C-H asymmetric stretching for R-CH_3), 2826 (C-H symmetric stretching for R-CH_3), 1430 (C-H asymmetric bending for R-CH_3), 1378 (C-H symmetric bending for RCH_3), 3083-3017 (C-H stretching frequency for aromatic region), 1563 (C-C skeletal stretching of phenyl nucleus), 1229 (C-H in plane bending for phenyl ring), 826 (C-H out of plane bending for 1,4-Disubstituted benzene ring), 2917 (C-H stretching frequency for ketone), 1732 (C=O stretching frequency for ketone in 5 membered saturated ring), 1064-1006 (C-N stretching frequency for tertiary amine), 723 (C-Cl stretching for monochlorinated aromatic compounds); MS: *m/z:* 344.08

Preparation of 3-(2-methylindolin-1-yl)-2-(4-nitrophenyl) thiazolidin-4-one (5).

Yield: 75 %; M.P.- 212-214 ºC; IR (cm^{-1}): 1606 (Ring stretching for Indoline), 1402 (Ring stretching modes for thiazolidinone ring), 871-650 (C-H out of plane bending for Thiazolidinone ring, several bands observed), 2960-2922 (C-H asymmetric stretching for R-CH_3), 2850 (C-H symmetric stretching for R-CH_3), 1433 (C-H asymmetric bending for R-CH_3), 1375 (C-H symmetric bending for RCH_3), 3088-3005 (C-H stretching frequency for aromatic region), 1583 (C-C skeletal stretching of phenyl nucleus), 1224 (C-H in plane bending for phenyl ring), 831 (C-H out of plane bending for 1,4-Disubstituted benzene ring), 2914 (C-H stretching frequency for ketone), 1739 (C=O stretching frequency for ketone in 5 membered saturated ring), 1074-1016 (C-N stretching frequency for tertiary amine), 1531-1525 (NO_2 asymmetric stretching frequency for aromatic Nitro group), 1303 (NO_2 symmetric stretching for aromatic NO_2 group); ^{1}H NMR (DMSO-d_6) δ ppm: 1.27- 1.28 (d, 3H), 4.47-4.52 (m, 1H), 2.69-2.74 (d, 1H), 3.39-3.46 (q, 1H), 7.05-7.07 (d, 1H, *J*=8 *Hz*), 7.13-7.16 (m, 2H), 6.79-6.83 (m, 1H), 7.37 (s, 1H), 7.64-7.66 (d, 2H, J value= *8 Hz*), 8.09-8.11 (d, 2H, J value= *8 Hz*), 5.37 (s, 2H); MS: *m/z:* 355.10;

CONCLUSION

The various thiazolidinones appended with 2-methyl indoline as a core fragment. Thiazolidinone, a saturated form of thiazoles with carbonyl group on fourth carbon, has been considered as a moiety of choice as it possesses a broad spectrum of pharmacological activities against several targets.

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