International Journal of Advanced Biotechnology and Research
ISSN 0976-2612, Online ISSN 2278–599X,
Vol5, Issue2, 2014, pp163-168
http://www.bipublication.com

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY STUDIES OF N'-(2-(4-OXO-2-SUBSTITUTED THIAZOLIDIN-3-YLAMINO) QUINAZOLIN-4-YL) ISONICOTINO HYDRAZIDE

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[Received-20/03/2014, Accepted-01/04/2014]

ABSTRACT:

Thiazolidinone moiety possesses several biological activities and it is essential precursor for microbiological studies even many other applications. In recent years, the literature has shown a great increase both in academic and in commercial research in the preparations, reactions and the physiological activities of these compounds. These observations served as an impetus for the extension of investigation in the field of synthesis of 4-thiazolidione derivatives in the hope of discovering compounds with good pharmacological properties. The peak of research activity is yet to find in this vast and interesting area of study; much more needs to be done and achieved. The synthesis and chemistry of 4-thiazolidinones using nonconventional, environment friendly procedures is investigated in this study.

Keywords: *Isoniazid, IR/NMR Spectroscopy, Antibacterial, Antifungal activity.*

[I] INTRODUCTION:

4-thiazolidinone is a derivative of thiazolidine with a carbonyl group at 4th position which belongs to an important group of heterocyclic compounds.The methylene carbon atom at fifth position of 4-thiazolidinone possesses nucleophilic activity and attacks an electrophilic center. The reaction product loses water, forming a 5-unsaturated derivative of the 4-thiazolidinone. The reaction occurs in the presence of a base and the anion of the 4-thiazolidinone is the attacking species [1]. The ease of formation of the anion and hence the degree of the nucleophilic activity is dependent not only on the electron-withdrawing effect of the adjacent carbonyl group, but also on the presence of other electron-withdrawing groups such as those attached to the second carbon atom [2]. The electron attraction of sulfur of 2-thione group is greater than that of the oxygen of a 2-carbonyl group.The nucleophilic activity of 5-methylene carbon atom of 2-aryl-4-thiazolidinone or 2-arylimino-4-thiazolidinone should be influenced by the nature of the substituents attached to the aryl group. The mobility of the hydrogen atoms in the methylene group depends much upon the electro-negativity

and co-planarity of substitution on the exocyclic nitrogen.The aldehydes, however, react only on one 4-thiazolidinone moiety to give the corresponding 5-unsaturated products. The condensation of aldehydes with 2-alkylor-aryl-4-thiazolidinones does not occur due to acetic acid and sodium acetate, possibly because of the decreased reactivity of the methylene group. The reactivity is increased due to presence of imino or thioxo groups at second position at 4-thiazolidinone. Three components substituted aromatic amines, substituted aromatic aldehydes and a mercapto acid are used to synthesize 4-thiazolidinone derivatives. These processes can be conducted in two ways, one pot (one step) and two step reactions [3-4].

4-thiazolidinone is a useful moiety for a variety of heterocyclic products including drugs [5-6], dyes and intermediates such as thiazol yellow, thioflavin T. ,thidiazuron [7], the uses of this class of chemicals (4-thiazolidinone derivatives) are as herbicides [8], insecticides [9-10] etc. The thiazolidinones moiety is also associatedwith broad spectrum of biological activities including antibacterial [11-12], antifungal,anti-inflammatory, hypnotic, anticonvulsant, antitubercular, antiviral, antihistaminic, anthelmintic, cardiovascular and anticancer. A number of 4-thiazolidinones derivatives were investigated for their inhibitory effects on the oxidation of the substrates of the tricarboxylic cycle and β-hydroxybutyrate by rat brain homogenatesfor respiratory activity [13].

[II] MATERIAL AND METHODS:

All the chemicals used were of pure grade (Merck and B.D.H). The melting points of all compounds were determined by open capillary method and were uncorrected.

[III] EXPERIMENTAL:

3.1. Preparation of 2,4-Quinazolinedione:

In a 1000ml beaker, a mixture of (20 gm, 0.146mole) of anthranilic acid, 700ml of warm water (40^0 c) and glacial acetic acid (11ml, 0.19mole) was stirred mechanically and allowed to cool to room temperature. A freshly prepared solution of (15gm, 0.185mole) of potassium cyanate in 50ml of water was then added drop wise with stirring over a period of 15 to 20 minutes. The resulting pasty mixture was stirred for 20 minutes and then (200gm, 5mole) of Sodium hydroxide was added slowly in small portion. During this addition the reaction mixture was kept below 40^0 c by cooling in a cold water bath. A clear solution was obtained momentarily, but in a sort time a fine granular precipitate of the hydrated mono sodium salt of benzoylene urea precipitate. After the mixture has cooled over night in an ice box, the precipitated sodium salt was collected on a Buckner funnel. The colorless salt was dissolved in 1 lit of hot water and the solution was filtered. The compound was precipitated by adding dilute sulfuric acid.(1:1) with vigorous stirring until the liquor was acidic to litmus the material was collected, washed with water and dried in an oven at 100 ^{0}C.

3.2. Preparation of 2,4-Dichloroquinazoline:

In a 250 ml R.B.F., a mixture of (20gm, 0.123mole) of 2, 4-quinazolinedione, 200ml of phosphorus oxychloride and of tri-n- propyl amine (59gm 0.226mole) refluxe for 30minutes to yield a clear solution and volatile liquid was removed by distillation. The remaining mass was added in to ice and isopropyl alcohol. The product was extracted from residue with (4x200 ml) portion of hot n-heptane containing 2% tri-n-propyl amine. The combine extracts, at room temperature was diluted with enough benzene to dissolved crystallized solid. The organic solution was washed with 400ml of 5% NaOH and three times with water. The solvent was removed in vacuo, and the residual solid was recrystallized from 2:1 ethyl acetate: n-heptane to give 12.1 gm. Of 2,4-dichloroquinqzoline as white needles. A second crop of product was obtained by reducing the mother liquor to one fouth the volume to give 6.7 gm. The combine yield of the two crops was 18.8 gm

3.3. Preparation of N'-(2-chloroquinazolin-4-yl)isonicotinohydrazide:

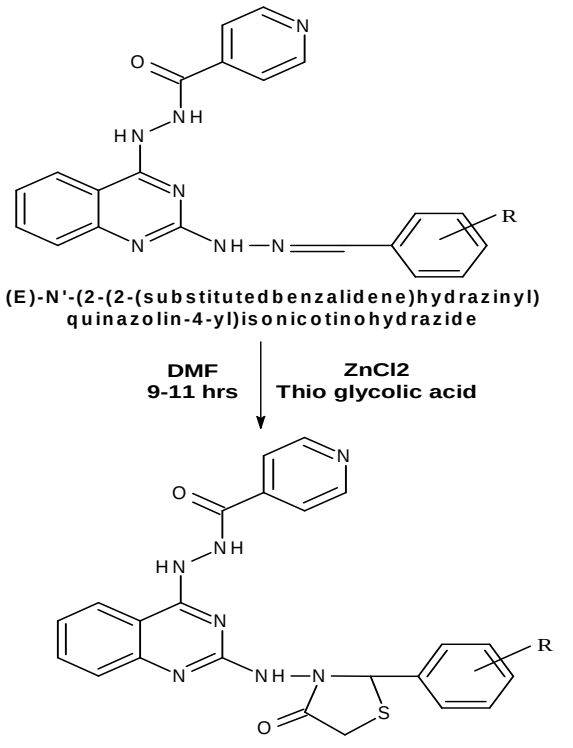
In 250 ml R.B.F., a solution of 2,4-dichloroquinazolin(0.01 mole) dry ether(20 ml)

was taken & added Isoniazid (0.01 mole) the mixture was stirred at room temperature for 24 hr, the ether was removed on a steam bath & the residue dissolved in approximately 150 ml of water. The Solution was made basic with 20 % aqueous NaOH & Extracted three times with chloroform. The Combined Chloroform Extract were washed once with water, once with saturated Sodium Chloride solution & then dried over magnesium sulphate. After removal of chloroform the residue was purified by recrystallization using Ethanol.

3.4. Preparation of N'-(2-hydrazinoquinazolin-4-yl) isonicotinohydrazide:

In a 250 ml R.B.F.,solution of N'-(2-chloroquinazolin-4-yl)isonicotinohydrazide. (0.01 mole) in DMF was taken & added Hydrazine hydrate (80%,0.01 mole).The reaction Mixture was Stirred at 110 ^{0} C for 18 hrs. The resulting mixture was cooled to room temperature, neutralized with ammonia. The Solid was filtered, washed, Dried & Recrystallised using ethanol.

Reaction Scheme



Where R =4-CH_3,3-CH_3-4-OH, 4-Cl, 2-NO_2, 2:4-Cl_2, 2-OCH_3, 4-NO_2, 4-H, 4-$N(CH_3)_2$,2OH

3.5. Preparation of (E)-N'-(2-(2-(substituted benzalidene) hydrazinyl) quinazolin-4-yl)isonicotino hydrazide:

In a 250 ml R.B.F., N'-(2-hydrazinoquinazolin-4-yl)isonicotinohydrazide (3.10 gm ,0.01 mole) in THF was taken & Substituted benzaldehyde(0.01 mole) and 1 drop of conc. H_2SO_4 were added & refluxed for 9 – 10 hrs. The completion of reaction was monitored by TLC Examination 1:1 (Hexane: ethyl acetate). After completing of reaction the flask was cooled over night and residue was filtered off. The solid thus separated was filtered, washed with water & recrystalised from ethanol.

3.6. Preparation of N'-(2-(4-oxo-2-substitutedthiazolidin-3-ylamino) quinazolin-4-yl) isonicotino hydrazide:

In a 250 ml R.B.F, (E)-N'-(2-(2-(substitutedbenzalidene) hydrazinyl) quinazolin-4-yl) isonicotino hydrazide (0.01 mole) and thiogylcolic acid (0.03 mole) were taken in DMF (25 ml) as a solvent. The reaction mixture was refluxed for 9-11 hr. After the completion of the reaction (monitored by TLC using xylene: ethyl acetate, 70:30) the excess of solvent was removed by distillation and cooled. The solid thus separated filetered, washed, dried and recrystallised from glacial acetic acid.

[IV] RESULTS AND DISCUSSION:

All the tested compounds have shown antibacterial activity to some extent. Among the tested compounds **2a** and **2c** showed very good activity against the tested organisms. Compounds **2b**, **2d** and **2e** are moderate antibacterial activity. The compounds **2b**, **2c** and **2i** showed good antifungal activity. All the compounds synthesized possess electron releasing groups, on both the aromatic rings. Therefore from the results it is evident that compounds having electron releasing groups like methyl, hydroxy and methoxy may be responsible for antibacterial and antifungal activities.

Table- 1: Characterization Table of N'-(2-(4-oxo-2-substitutedthiazolidin-3-ylamino) quinazolin-4-yl) isonicotino hydrazide

No	R	Molecular formula (M. wt.)	Yield (%) (per./ hrs.)	M.P. ^{0}C.
2a	4-CH_3	$C_{24}H_{21}N_7O_2S$ (471.54)	75 (9.5)	176-77
2b	3-0CH_3,4-OH	$C_{24}H_{21}N_7O_4S$ (503.54)	68 (10)	220-21
2c	2-NO_2	$C_{23}H_{18}N_8O_4S$ (502.51)	76 (9.5)	198-99
2d	4-Cl	$C_{23}H_{18}ClN_7O_2S$ (491.95)	62 (10.5)	205-06
2e	2,4-$(Cl)_2$	$C_{23}H_{17}Cl_2N_7O_2S$ (526.40)	69 (10)	232-33
2f	2-OCH_3	$C_{24}H_{21}N_7O_3S$ (487.54)	72 (11)	186-87
2g	4-NO_2	$C_{23}H_{18}N_8O_4S$ (502.51)	60 (11)	193-94
2h	4-H	$C_{23}H_{19}N_7O_2S$ (457.51)	84 (9)	157-58
2i	4-$N(CH_3)_2$	$C_{25}H_{24}N_8O_2S$ (500.58)	71 (11)	201-02
2j	2-OH	$C_{23}H_{19}N_7O_3S$ (473.51)	65 (9)	171-72

4.1. ^{1}H NMR Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy is one of the latest physical methods of investigating organic compounds. The scale of the spectrum is usually marked in parts per million (ppm) of the applied field or in frequency units (Hz). ^{1}H-NMR spectra were recorded on Bruker WM 400FT MHz NMR instrument using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal reference. The data of compound (4a) is summarized in table -2.

Table-2

Signal position (δ ppm)	Inference
3.57	–CH2
6.19	–CH
8.00	-NH (a)
8.35	-NH(b)
9.58	-NH(c)
6.79 to 7.75	Aromatic Protons

4.2. Infrared spectra

The systematic interpretation of the infra - red spectrum is based upon the empirical data obtained by assigning infra-red absorption values to the structural units a characteristic of different structural units. Infra - red spectra were recorded in KBr on a Shimadzu FTIR spectrophotometer. The data of the structure is summarized in table-3 as below.

Table-3:

Adsorption	PN-58	PN-59
N-H (st)	3380.62	3429.77
-CH_3	2958.75	-----
-NO_2	-----	1251.09
-C=O	1674.39	1660.40
-C-S-C	770.42	733.29
-N-C=O	1634.85	1638.71
-C=N(st)Quinazoline	1604.48	1599.18
N-C-N (st)Quinazoline	1365.35	1349.44
Ar (C=C)	1490.70	1530.72
In plane Ar-H	1140.68	1137.79
Ar-H (b) Vib.	854.79	826.34
Out plane Ar-H	681.23	690.39

4.3. Antimicrobial activity

The examination of antimicrobial activity of organic compound and its all substitution reveals that the compound is moderately more or less active against various organisms. The synthesized compounds were screened for their antibacterial activity using *S.aureus, E. coli, P.aeruginosa and S. pyogenus* (Table-4). Control experiment was carried out under similar condition by using ampicillin and chloremphenicol as standard. The inhibition zone measure in mm showed that compound **2c** and **2i** were more active than other compounds

tested against the above microbes. Anti-bacterial activity of Compounds was investigated via the broth dilution method [14-16].

Table-4 Antimicrobial activity of compound

Code No	*S. aureus*	*P.aeruginosa*	*E. coli*	*S. pyogenus*
4a	250	100	250	200
4b	200	100	250	100
4c	125	62.5	200	100
4d	200	125	250	100
4e	500	125	100	250
4f	200	250	100	250
4g	250	200	200	500
4h	200	250	125	250
4i	125	100	200	200
4j	62.5	200	250	100
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50

4.4. Anti-fungal activity

The investigation of antifungal activity of Compound4a-4j was carried out with the stiff plate agar diffusion method [17] against *C.albicans,A.niger and A.clavatus.* The amount of microbial cells was 109c.f.u. /ml. Incubation period was 24 h at 35 °C for bacteria. Antibiotics nystatin and greseofulvin were used as standards. The bacterial cultures, standards, and obtained substances in 5 mg/ml concentration were streaked across grooves and then allowed to dif-fuse in the agar nutrient plate (Table-5).

Table-5 Antifungal activity of compound

Code No	*C.albicans*	*A.niger*	*A.clavatus*
4a	500	>1000	250
4b	100	1000	500
4c	100	250	125
4d	250	1000	100
4e	500	250	500
4f	1000	100	1000
4g	1000	250	1000
4h	500	1000	100
4i	>1000	100	125
4j	500	500	250
Nystatin	100	100	100
Greseofulvin	500	100	100

[V] CONCLUSION:

The work has approached towards the synthetic and biological approach of these wonder molecules. Anti-bacterial property of the synthesized compounds has exhibited very good inhibition; the compounds 2c and 2i have exhibited outstanding activity towards *S.aureus, E. coli, P.aeruginosa and S. pyogenus.* Compound 2a, 2b and 2i shows good activity against *P.aeruginosa*. compound 2b, 2c, 2d, 2f, 2h, 2i and 2j shows good activity against S.aureus. But the systematic substitution at various position and other derived compounds have shown remarkable antifungal properties. The compounds 2b, 2c and 2i have exhibited god activity towards *A.niger, A.clavatus* and C. *albicans.* Compound 2b and 2c shows good activity against C. *albicans* where compound 2f and 2i shows good activity against *A.niger*. The remaining compounds have shown poor antifungal activity indicating less biological importance for a synthetic chemist.

[VI] ACKNOWLEDGEMENT:

The uthors are thankful to Department of Chemistry, Arts, Science & Commerce College, Kholwad, Surat for providing laboratory facilities.

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