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PharmTech

International Journal of PharmTech Research
CODEN(USA): IJPRIF ISSN : 0974-4304
Vol.1, No.2, pp 252-255 , April-June 2009

Synthesis of Substituted Sulphaquinoxalinones as Anti-Mycobacterium tuberculosis agents.

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Abstract : 3-[(6'-sulphaneoamidoquinoxaline-2',3'-(1'*H*,4'*H*)-dione)-2-(substitutedphenyl)]-4-oxo- thiazolidine (**3a-f**) have been synthesized by cyclisation of N^1 –(substitutedbenzylidine amino)-6-(quinoxaline-2,3(1*H*,4*H*)-dione sulphanamide (**2a-f**) with thioglycolic acid in presence of anhydrous zinc chloride and dry benzene. N^1–(substituted benzylidine amino) -6-(quinoxaline-2,3(1*H*,4*H*)-dione sulphanamide (**2a-f**) were obtained by reaction of 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl hydrazide with various substituted aryl aldehydes in methanol. 2,3-Dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl hydrazide was also treated with several aryl iso-thiocyanates to yield N^1-[(6'-sulphaneo amido quinoxaline-2',3'(1'*H*,4'*H*)-dione)-N^3-(*p*-substituted phenyl) thiocarbamides (**4a-e**). The constitution of synthesized compounds was supported by IR, ^{1}H NMR, Mass and elemental analysis. All the compounds were subjected to preliminary *in-vitro* evaluation for anti-tubercular activity against *Mycobacterium tuberculosis* H_{37}RV strain.

Key Words: Quinoxaline-2,3(1*H*,4*H*)-diones, anti-tubercular activity

Introduction

Quinoxalines and their derivatives display diverse pharmacological activities. For example some display antibacterial[1], antifungal[2], anticancer[3], anti-tubercular[4], anti-malarial[5], antidepressant[6], anti-thrombotic[7], analgesic and anti-inflammatory[8], AMPA receptor antagonist activity[9]. Encouraged by these observations, it was thought worthwhile to synthesize some new titled compounds and screen them for their possible anti-tubercular activity.

In present work quinoxalinedione has been subjected to chlorosulfonation to yield 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl chloride which on reaction with hydrazine hydrate in presence of dry pyridine gave 2,3-dioxo-1,2,3,4-tetra hydro quinoxaline-6-sulfonyl hydrazide. Reaction of sulfonyl hydrazide with various substituted aromatic aldehydes in methanol yields N^1-(substituted benzylideneamino)-6-(quinoxaline-2,3(1*H*,4*H*)-dione)sulphanamide (**2a-f**), which was further cyclised with thioglycolic acid in presence of anhydrous zinc chloride and dry benzene to give 3-[(6'-sulphaneoamidoquinoxaline-2',3'-(1'*H*,4'*H*)-dione)-2-(substitutedphenyl)]-4-oxo-thiazo-lidine (**3a-f**), moreover sulfonyl hydrazide was also treated with several aryl iso-thiocyanates to yield N^1-[(6'-sulphaneoamidoquinoxaline-2',3'(1'*H*,4'*H*)-dione)—N^3-(p-substituted phenyl)thiocarbamides (**4a-e**).

Materials and methods

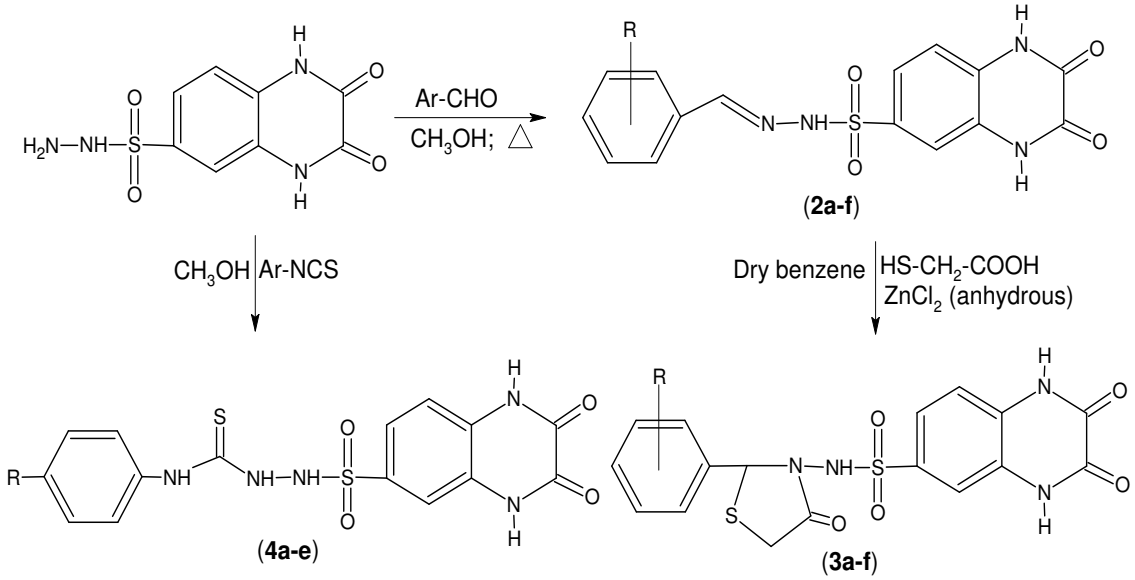
All the melting points were recorded in open capillary tubes using paraffin bath and are uncorrected. Purity of the compounds was checked by TLC using silica gel-G plates and benzene-acetone (3:1) as solvent. IR spectra (KBr disc) were recorded on Perkin Elmer RXI-FTIR system. Proton Magnetic Resonance spectra (^{1}HNMR) were recorded on Bruker AC-300F NMR spectrometer (300MHz) using $CDCl_3$ and DMSO-d_6 as solvent and Tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Jeol SX 102/DA-6000 mass spectrometer/ data system using Argon / Xenon (6Kv, 10mA) as FAB gas. The accelerating voltage was 10 kV and the spectra were recorded at room temperature using *m*-nitrobenzyl alcohol (NBA) matrix. Elemental analysis was carried out with Carlo Erba 1108 analyzer; all the compounds gave satisfactory elemental analysis within ±0.4% of the theoretical values.

Experimental

Synthesis of N^1-(substituted benzylideneamino)-6-(quinoxaline-2,3(1*H*, 4*H*)-dione) sulphanamide (2a-f):

2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl hydrazide (0.01 mol) was dissolved in methanol (15 ml) and various substituted aromatic aldehyde (0.011 mol) in methanol (40 ml) was added with shaking. The reaction mixture was refluxed for a period of 03 hrs; reaction was monitored by TLC. After completion of reaction the reaction mixture was concentrated under reduced pressure and cooled in ice bath, solid obtained was filtered, washed with cold water, dried and crystallized from methanol and acetic acid mixture. Compound (**2d**) showed **I.R.** (KBr cm^{-1})**:** 3434 (NH, str), 1704 (C=O, str), 1601 (-CH=N- str), 1400 (SO_2, symm.), 1164 (SO_2, asymm.). **^{1}H NMR** (DMSO-d_6) δ **:** 10.05 (s, 1H, -CH=N-), 10.01 (s, 2H, -NH-CO- quinoxaline ring), 7.02 – 7.95 (m, 7H, Ar-H), 2.95 (s, 1H, -NH-)**. MS** m/z (%)**:** 429 (14), 417 (27), 397 (20), 392 (34), 391 (100; base peak)**.**

Scheme:



Synthesis of 3-[(6'-sulphaneoamido quinoxaline-2',3'(1'*H*,4'*H*)-dione)-2-(substit utedphenyl)-4-oxo-thiazolidine (3 a-f):

To a mixture of N^1-(substituted benzylidene amino)-6-(quinoxaline-2,3(1*H*, 4*H*)-dione) sulphanamide (0.01 mol) in dry benzene (20 ml), thioglycolic acid (0.015 mol) and a catalytic amount of anhydrous zinc chloride was added and the reaction mixture was refluxed for 12 hrs. Solvent was evaporated under reduced pressure and separated residue was neutralized by saturated sodium bicarbonate solution, the precipitated solid was filtered, washed with cold water, dried and crystallized from acetic acid. Compound (**3d**) **I.R.** (KBr cm^{-1})**:** 3440 (NH, str), 2933 (CH, str, aromatic), 1700 (-C=O- str), 1480 (SO_2, symm.), 1250 (SO_2, asymm.). **^{1}H NMR** (DMSO-d_6) δ **:** 7.89 (s, 2H, -NH-CO-quinoxaline ring), 7.23 – 7.66 (m, 7H, Ar-H), 3.33 (s, 1H, CH-thiazolidinone ring). 2.99 (s, 2H, -S-CH2-thiazolidinone ring), 2.70 (s, 1H, -NH-). **MS** m/z (%): 490 (34), 468 (34), 461 (50), 460 (100, base peak)**.**

N^1-[(6'-sulphaneoamidoquinoxaline-2',3'(1'*H*,4'*H*)-dione)—N^3-(*p*-substituted phenyl)thiocarbamides 4 (a-e):

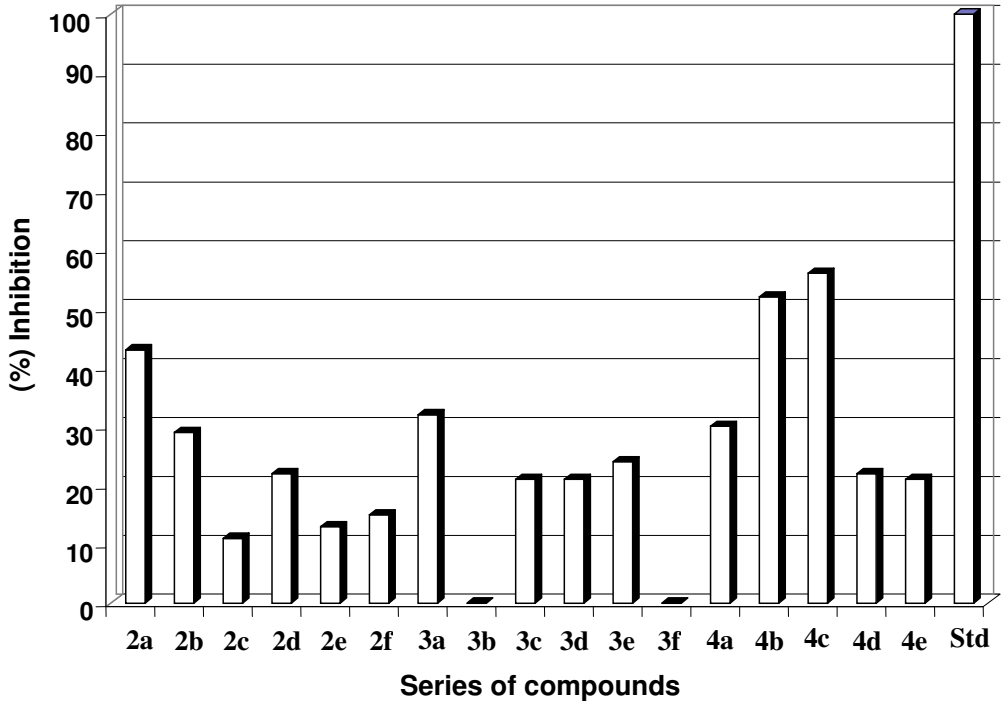
A mixture of 2,3-dioxo-1,2,3,4-tetrahydro quinoxa line-6-sulfonyl hydrazide (0.01 mol) and *p*-substituted aryl-isothiocyanates (0.011 mole) in methanol (50 ml) was refluxed on a water bath for 03 hrs. The reaction mixture was then concentrated and cooled in ice-bath, thus separated crystalline solids were filtered, dried and crystallized from methanol / acetic acid. Compound (**4b**) **I.R.** (KBr cm^{-1})**:** 3234 (NH, str), 2947 (C-H, str), 1838 (-CO-NH- str), 1309 (SO_2, symm.), 1280 (C=S,), 1137 (SO_2, asymm.). **^{1}H NMR** (DMSO-d_6) δ**:** 9.65 (s, 2H, -NH-CO- quinoxaline ring), 7.31 – 7.68 (m, 7H, Ar-H), 3.99 (s, 1H, -NH-C=S), 2.95 (s, 2H, -NH-NH_2)**. MS** m/z (%)**:** 218 (15), 203 (66), 201 (98), 202 (100, base peak)**.**

Table 1: Physical data and anti-tubercular activity data of synthesized compounds.

Compd. No.	R	M.P. (^{O}C)	Yield (%)	(%) N Calcd (Found)	(%) S Calcd (Found)	% Inhibition against H_{37}RV strain
2a	H	254	40	16.27 (16.30)	9.31 (9.28)	43
2b	2-OH	291	45	15.55 (15.56)	8.90 (8.89)	29
2c	2-Cl	263	35	14.78 (14.82)	8.46 (8.49)	11
2d	4-Cl	254	60	14.78 (14.80)	8.46 (8.51)	22
2e	2-OCH_3	262	40	14.96 (14.99)	8.56 (8.61)	13
2f	4-OCH_3	296	55	14.96 (15.01)	8.56 (8.59)	15
3a	H	279	48	13.38 (13.42)	15.32 (15.35)	32
3b	2-OH	307	40	12.89 (12.92)	14.76 (14.76)	00
3c	2-Cl	284	28	12.37 (12.41)	14.16 (14.20)	21
3d	4-Cl	317	55	12.37 (12.39)	14.16 (14.21)	21
3e	2-OCH_3	277	50	12.49 (12.52)	14.30 (14.28)	24
3f	4-OCH_3	319	68	12.49 (12.50)	14.30 (14.32)	00
4a	H	267	56	17.89 (17.94)	16.38 (16.35)	30
4b	Cl	194	65	16.44 (16.48)	15.06 (15.09)	52
4c	Br	204	61	14.89 (14.91)	13.64 (13.61)	56
4d	CH_3	238	48	17.27 (17.30)	15.82 (15.80)	22
4e	OCH_3	252	54	16.62 (16.64)	15.22 (15.20)	21

Anti-tubercular screening: Anti-tubercular activity of synthesized compounds was determined by Micro plate Alamar Blue Assay (MABA) method against H_{37}RV strains of *Mycobacterium tuberculosis* at a concentration of 6.25 µg/ml. DMSO was used as solvent. Isoniazid (0.025 µg/ml) and Rifampicin (0.125 µg/ml) were used as standards and the results are reported in Table 1 and also presented in figure 1.

Figure 1: Anti-tubercular activity of synthesized compounds



Results and discussions

The purity of all the synthesized compounds was checked by thin layer chromatography and all the compounds gave satisfactory elemental analysis within ± 0.4% of the theoretical values. The constitution of synthesized compounds was confirmed with IR, ^{1}H NMR and Mass spectral analysis. The *in vitro* anti-tubercular screening against $H_{37}RV$ strains of *Mycobacterium tuberculosis* reveals that compounds **4c** & **4b** were found to show highest activity amongst all the synthesized compounds whereas it was found to be less than the standards used. Compounds **3b** & **3f** where totally devoid of any anti-tubercular activity, whereas rest of the compounds were found to possess moderate activity.

Acknowledgement

Authors are thankful to TAACF, Southern Research Institute, Federick, USA, for providing anti-tubercular screening reports, to R.S.I.C, C.D.R.I, Lucknow for spectral and elemental analysis.

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