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Synthesis and anti-microbial activity of few derivatives of 2-mercapto-3-phenyl-quinazolin-4(3*H*)-one

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ABSTRACT

2-Mercapto-3-phenyl-quinazolin-4(3*H*)-one have been prepared by the reaction between anthranilic acid and phenyl thiourea. The sodium salt of 2-mercapto-3-phenyl-quinazolin-4(3*H*)-one on condensing with substituted aroyl chloride yielded thioesters of 3-phenyl-quinazolin-4(3*H*)-one. All the synthesized thioesters were screened for their antimicrobial activity against *Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis.* Some of the compounds showed good activity by taking Norfloxacin as standard.

KEYWORDS

Anthranilic acid;
Thioesters;
Antimicrobial activity.

INTRODUCTION

Compounds bearing the quinazoline moiety are endowed with various types of biological activities. Quinazoline derivatives have been reported as antihelmintic[1], CNS depressant[2], MAO inhibitor[3], sympatholytic[4], antibacterial[5], antitubercular[6], antimalarial[7], antiulcer[8], anti-inflammatory[9], antifungal activity[10]. While 2-mercapto derivatives of quinazoline are well known for their antibacterial[11], antitubercular[12] activity.

The literature survey reveals that a number of 2-mercapto-3-phenyl-4-(3*H*)-quinazolin as potential phamacophore. So far biological activities are concerned including antimicrobial activities. Therefore the present work of the synthesis and antibacterial evaluation of substituted 2-mercapto-3-phenyl-4(3*H*)-quinazolin was taken.

EXPERIMENTAL

All the melting points are taken on superfit melting point apparatus with the help of open capillary tubes. The I.R spectra in KBr were recorded on a Perkin-Elmer 157 Spectrometer (ν_{max} in cm^{-1}) and ^{13}C NMR spectra were recorded on Bruker at 300MHZ Spectrometer using $CdCl_3$ and DMSO as the solvent. The homogeneity and purity of the compounds were ascertained by TLC on Silca gel G-Plates and the spots were visualized by using iodine vapours.

Synthesis of *m*-nitro phenyl thiourea (2a)

A mixture of *m*-nitroaniline (0.1mol) and ammonium thiocynate (0.1mol) was fused on oil bath at 150-170°C for two hr. Residue was separated. Recrystallised from distilled water.

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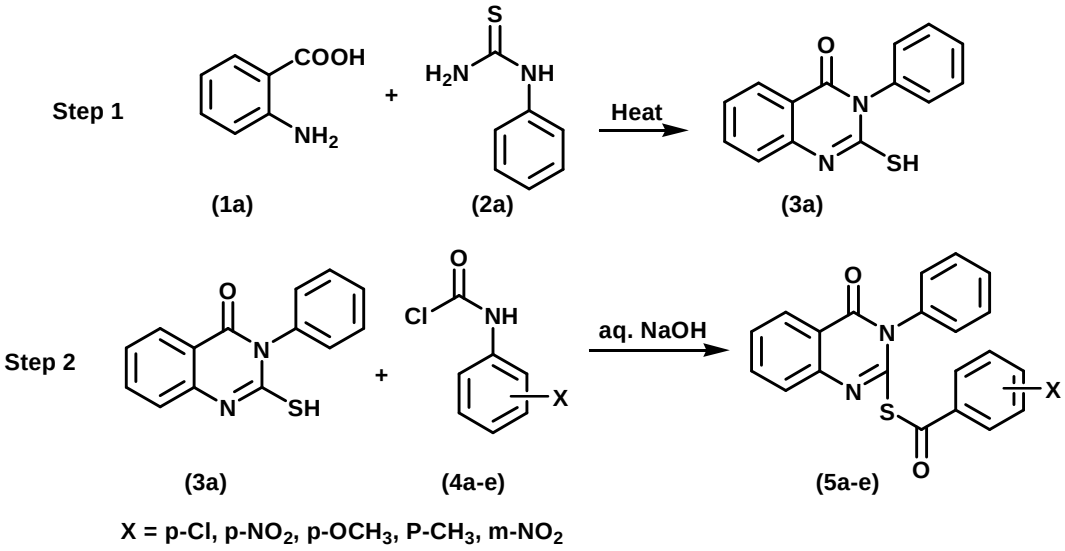

Scheme 1

Synthesis of 2-mercapto-3-phenyl-4(3*H*)-quinazolinone (3a)

A mixture of anthranilic acid (0.1 mol) and N-phenyl thiourea (0.1 mol) was heated on the oil bath at 150-160°C for 2 hr after cooling; it was treated 4 to 5 times with hot 5% sodium hydroxide to completely extract out the thiol. The filtrate was cooled and neutralized with hydrochloric acid and resulting solution was filtered off. The synthesized compound was purified by solubilising in DMF and then precipitated by water.

Synthesis of aroyl chlorides (4a-e)

Mixed (0.01mol) of pure *p*-nitro benzoic acid and (0.01mol),of redistilled thionyl chloride in 100 ml round bottom flask. Fitted the flask with a double surface reflux condenser carrying a calcium chloride guard tube and connected the later to an adsorption device. Heated the flask on water bath with occasional shaking for 1 hr or until the evolution of hydrogen chloride and sulphur dioxide almost ceased.

The mixture was allowed to cool and it was transferred cautiously to a claisen flask connected with a water cooled condenser and a receiver. Excess of thionyl chloride was distilled off (b.p.77°C) and the distillation was continued until the temperature raised rapidly to about 120°C, this assured that all thionyl chloride was removed. It was allowed to cool and the precipitate was collected.

The other aroyl chlorides were similarly prepared

Synthesis of 2-mercapto-3-phenyl-4(3*H*)-quinazolinone (5a-e)

In aqueous solution of sodium hydroxide, 2-thio-3-phenyl-4(3H)-quinazolinone (0.004 mole) was added and resulting mixture was stirred until solution was affected. Aroyl chloride (0.005) mole was then added and the solution was stirred for one hour at 23-25°C,after cooling of the resulting mixture to 0°C the product was removed by filtration, washed with distilled water and dried and recrystallised from DMF.

In-vitro antibacterial screening[13,14]

Most of the new synthesized compounds were tested for their antimicrobial activity *in-vitro* against bacteria (*Pseudomonas aeruainosa, Staphylococcus aureus, Bacillus subtils)* employing the nutrient agar disc diffusion method at 500 µg/ml concentration using Norfloxacin as standard drug. The screening results present in TABLE 1.

RESULT AND DISCUSSION

In summary we have synthesised a series of six quinazoline derivatives as potential antibacterial agents. All synthesised compounds have shown mild to good activity against pathogenic bacteria. Compound no. Vc,Vd, Ve, showed good activity. Compounds were more active against gram positive bacteria.

TABLE 1 : Physical parameters for synthesized 4(3*H*)-quina- zolinone derivatives

S.N	Code No.	% Yield	M.P.	Mol. wt	% Nitrogen		% Sulfur		Zone of inhibition in (mm)		
					(%) calculated	(%) found	(%) calculated	(%) found	*S.aureus*	*P.airuginosa*	*B.subtilis*
1	3a	88.5	250	254	10.89	9.47	12.45	11.61	8	9	6
2	5a	90	280	403	10.37	7.39	7.9	7.12	10	9	7
3	5b	70	290	403	10.37	11.53	7.9	6.73	9	10	9
4	5c	85	205	388	7.18	5.46	8.20	7.80	11	9	8
5	5d	80	270	392 .5	7.97	8.62	8.12	8.34	10	11	7
6	5e	68	280	372	7.49	7.21	8.5	8.4	9	10	8

Spectral data of compounds

3a: IR(cm^{-1}) 3246, 3135, 3068, (Ar, C-H) 2362 (S-H), 1955 (Overtone band), 1663(C=O), 1488(C=C), 1267(C-N), 1228,1197 (C=N), 788 (Out of plane bending). ^{13}C NMR (δ ppm) 117.12, 125.42, 127.42, 128.50, (C of the N-Ar) 135.54, 135.94, 139.24, 139.87, 160.59, 176.52 (C of Quinazoline ring).

5a: IR(cm^{-1}) 3220 (C-H, Ar), 1954 (Overtone of Ar), 1663(C=O), 1621(C=O), 1298(C-N), 758, 719 (C-S), 690 (Out of plane bending). ^{13}C NMR (δ ppm) 116.14, 116.35, 124.42, 127.01, 127.84, 128.50 (C of N-Ar), 128.79, 129.28, 135.54, 139.24, 139.96, 160.37, 176.59, (C of Quinazoline Ring).

5b: IR(cm^{-1}) 3244, 3220, 3134, 3068 (C-H), 1954 (Overtone band) 1663 (C=O of Quinazoline), 1621 (C=O of Thioester), 1531 (N=O), 1487 (C=N), 1349 (N=O), 1299 (C-N), 799, 758, 719, 690 (Out of plane bending). ^{13}C NMR (δ ppm) 106.5, 106.4, 114.90, 117.20, 118.25, 118.43, 119.46 (C of N-Ar), 119.72, 120.35, 120.51, 122.95, 123.96 (C of S-Ar), 124.43 (C of Thio Ester), 125.65, 126.05, 129.86, 130.47, 150.56, 167.00 (C of Quinazoline ring).

5c: IR(cm^{-1}) 3247, (C-H Ar) 2979, 2840, (C-H, CH_3), 2364, 1709 (Overtone band), 1664 (C=O), 16049 (C=O), 1511, 1462, 1423 (C-H Bend), 1367, 1257 (C-O,Ar), 1167 (C-O CH_3), 923, 844, 769, 694 (Out of plane bending), 619 (C-S). ^{13}C NMR (δ ppm) 111.961, 113.643, 115.939, 122.471, 123.278, 124.196 (C of Ar), 127.546, 128.199, 128.680, 130.224, 130.884 (C of Quinazoline), 131.819, 135.359, 163.162, 167.373, 176.358 (C of S-Ar).

5d: IR(cm^{-1}) 3209, 3031 (C-H), 2362, 1787 (Overtone band), 1687 (C=O), 1620 (C=O), 1487, 1403 (C=C), 1321(C=N), 1228 (C-N), 849, 759, 649 (Out of plane banding), 619 (C-S), 471 (C-Cl). ^{13}C NMR (δ ppm) 116.19, 116.41, 124.44, 126.76, 127.78, 128.45, (C-of N-Ar) 129.05, 125.25, 130.11, 132.51, 135.60 (C of Quinazoline ring), 139.44, 140.02, 160.26, 176.52 (C of S-Ar).

5e: IR(cm^{-1}) 3446, 3242, 3133 (C-H), 2972 (C-H, CH_3), 2364, 1802 (Overtone band), 1665 (C=O), 1617 (C=O), 1576 (C-N), 1408 (C=N), 923 (C-H Bend), 839, 800, 756 (Out of plane banding), 690 (C-S). ^{13}C NMR (δ ppm) 21.087, 115.666, 115.922, 123.899, 127.288, 128.601 (C-of N-Ar), 128.961, 129.200, 135.039, 138.940, 139,522 (C of Quinazoline ring), 142.602, 159.740, 167.500, 176.076 (C of S-Ar).

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