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Synthesis of 2-Mercapto Substituted Quinazolin-4(3*H*)-One Derivatives using *β*-Cyclodextrin in Aqueous Medium

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Abstract: *An expedient, mild and highly efficient green synthesis of 3-mercapto Quinazolinone derivatives were synthesized using β-cyclodextrin as a phase transfer catalyst in the aqueous medium. 3-mercapto Quinazolinones employed with halo-acyl/halo-alkyl groups in β-cyclodextrin/water medium obtained thio-ethers. The resulting compounds anti-bacterial studies were carried out against Gram-ve and Gram+ve bacteria.*

Keywords: 3-Mercapto Quinazolinone, Halo Alkyl, *β*-Cyclodextrin, Anti Bacterial

I. Introduction

Quinazolinones have enormous applications in therapeutical actions like antimicrobials[1-4]. Researchers dogged many remedial actions such as anti-inflammation[5], anti-bacterial[6-7], anti-Alzheimer's[8], anti-cancer[9-10], anti-oxidation[11], and anti diabetes[12]. This back ground encouraged us to focus on synthesis of substituted Quinazolinones.

Environment concern, aqueous phase organic synthesis attracted the attention of chemists and many research publications witnessed that substantial progress in green synthesis. *β*-Cyclodextrin (*β*-CD) has emerged as an inexpensive, mild and environmentally compatible reaction media in organic transformations[13-15]. Herein, we spotlighting on *β*-cyclodextrin phase transfer catalysis in aqueous medium synthesis of 3-mercapto Quinazolinone derivatives.

II. Experimental Material and Methods

TLC: Pre coated silica-gel plates (Merck) were used and 60-120 silica gel was used for column chromatography. Fischer-Johns instrument was used for melting points. For spectral information: Thermo Nicolet Nexus 670 FT-IR spectrometer for IR spectrum using KBr reference. ^{1}H NMR spectra using Bruker Avance 400 and ^{13}C- NMR recorded on Innova 75 MHz spectrometer using $CDCl_3$ solvent. Fining MAT 1020 mass spectrometer for ESI-MS.

2.1 General Procedure

Scheme.1: Synthesis of 2-((2-oxo—phenylethyl) thio)-3-phenylquinazolin-4-(*3H*)-one:

β-cylodextrin (1.135g, 1 mmol) dissolved in H_2O (10 mL) stirred with heating until clear solution obtain. 2-mercapto-3-phenyl substituted Quinazolin-4-one (**4**) (1.0 mmol) and phenacyl bromide (**5**) (1.5 mmol) was added in one pot. The reaction mixture stirred for 12 h at 36 ºC temperature (reaction status monitored using TLC). After the reaction over *β*-CD filtered and the product extracted with ethyl acetate followed by evaporation. Purification of compound finished on silica gel using MeOH:$CHCl_3$ as mobile phase lead to Quinazolin-4-(*3H*)-one derivatives (**6a&6b)**.

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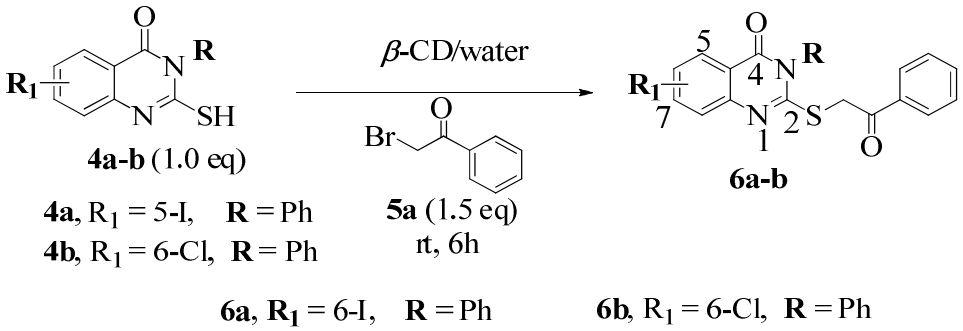
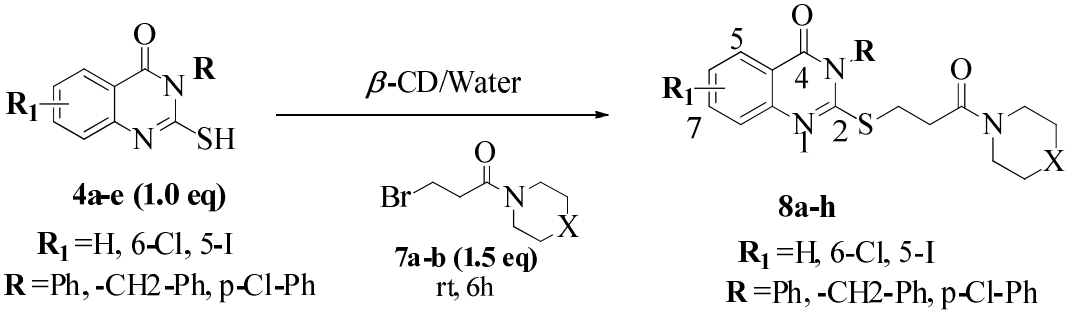


Scheme.2: synthesis of 2-((3-oxo-3-(alkyl/aryl-1-yl) alkyl) thio)-3- substituted Quinazolin-4- (3*H*)-ones (**8a-8h**):

β-cyclodextrin (1.135g, 1mmol) dissolved in few water by stirred with heating at 50 °C till the apparent solution obtain. 2-mercapto-3-substituted Quinazolin-4(3*H*)-one (**4**) (1.0 mmol) and amido-alkyl bromide (**5**) (1.5 mmol) taken in one pot and stirred the reaction mixture for 12 h at 36 ºC temperature. The final product extracted using ethyl acetate followed by evaporating the solvent and purification done on silica gel (60-120 mesh) using MeOH: $CHCl_3$ lead to mercapto Quinazolin-4-(3*H*)-one derivatives (**8a-h**):



2.2 Spectral Data:

5-Iodo-2-((2-oxo-2-phenylethyl) thio)-3-phenylquinazolin-4(3*H*)-one (6a):

Yield: 85%, mp: 187-189 °C, ^{1}H NMR: *δ*= 8.10 (s, 1H), 7.70-782 (s, 2H), 7.45-7.50 (4H), 7.40-7.44 (2H), 7.31 (1H), 7.26-7.29 (8H), 4.33 (2H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 195, 168, 165, 145, 140, 139, 135, 134, 132, 131, 129, 122, 98, 36; IR (KBr, cm^{-1}): 3245, 1698, 1605, 1552. ESI-MS $[M+H]^+$ *m/z*. 496.

6-Chloro-2-((2-oxo-2-phenylethyl) thio)-3-phenylquinazolin-4(3*H*)-one (6b):

Yield: 85%, mp: 212-214 ºC, ^{1}H-NMR: *δ*= 8.10 (s, 3H), 6.80 (1H), 6.55-6.65 (6H), 6.40-6.55 (5H), 7.0 (s,1H), 4.7 (2H). ^{13}C-NMR ($CDCl_3$, 75MHz) *δ*: 194, 165, 162, 147, 138, 136, 134, 132, 131, 129, 128, 126, 124, 122, 120, 36; IR (KBr, cm^{-1}): 2930, 1711, 1605, 1496. ESI-MS $[M+H]^+$ *m/z*. 406.

3-(4-Chlorophenyl)-2-((3-oxo-3-(piperidin-1-yl) propyl) thio) quinazolin-4(3*H*)-one (8a):

Yield: 85%, mp: 146-148 ºC, ^{1}H- NMR: *δ*= 7.98 (s, 1H), 6.48 (3H), 6.46 (1H), 7.28 (1H), 7.22 (2H), 3.40 (6H), 2.30 (4H), 1.55 (2H), 1.38 (4H); ^{13}C-NMR ($CDCl_3$, 75MHz) *δ*: 175, 165, 160, 149, 134, 132, 130, 129, 127, 125, 124, 122, 121, 48, 30, 28, 24, 22; IR (KBr, cm^{-1}) 3430, 1730, 1600, 1512; ESI-MS $[M+H]^+$ *m/z*. 427.

2-((3-oxo-3-(piperidin-1yl) propyl) thio)-3-phenylquinazolin-4(3*H*) -one (8b):

Yield: 85%, mp: 143-145 ºC; IR: 3377, 1710, 1595, 1499; ^{1}H-NMR: *δ*= 7.98 (2H), 7.80 (1H), 7.45 (s, 2H), 6.52 (2H), 6.32 (4H), 3.40 (4H), 3.30 (2H), 2.73 (2H), 1.50 (2H), 1.39 (4H); ^{13}C-NMR ($CDCl_3$, 75MHz) *δ*: 176, 165, 162, 145, 132, 130, 129, 128, 127, 125, 123, 122, 121, 50, 34, 27, 25, 23; ESI-MS $[M+H]^+$ *m/z*. 393.

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6-Chloro-2-((3-oco-3-(piperidin-1-yl) propyl) thio)-3-phenylquinazolin-4(3*H*) -one (8c):
Yield: 80%; mp: 180-182 °C; IR (cm^{-1}): 2925, 1708, 1605, 1541, 1408; ^{1}H-NMR: δ= 7.90 (s,1H), 7.65 (s,1H), 6.40-6.56 (6H), 3.30-3.48 (9H), 2.75 (2H), 1.54 (2H), 1.38-1.46 (4H); ^{13}C-NMR ($CDCl_3$, 75MHz) δ: 174, 168, 165, 145, 137, 132, 131, 130, 129, 123, 122, 120, 49, 32, 28, 25, 22; ESI-MS $[M+H]^+$ *m/z*. 427.

3-Benzyl-2-((3-oxo-3-(piperidin-1-yl) propyl) thio) quinazolin-4(3*H*) -one (8d):
Yield: 85%; mp: 138-140 °C; IR (cm^{-1}): 3080, 1702, 1600, 1518, 1402; ^{1}H-NMR: δ= 7.98 (1H), 7.80 (s,1H), 6.40 (1H), 6.22-6.35 (6H), 5.70 (2H), 3.46 (6H), 2.80 (4H), 1.58 (2H), 1.48 (4H); ^{13}C-NMR ($CDCl_3$, 75MHz) δ: 180, 162, 156, 150, 142, 134, 131, 129, 128, 126, 123, 121, 48, 43, 34, 29, 27, 25; ESI-MS $[M+H]^+$ *m/z*. 407.

3-(4-Chlorophenyl)-2-((3-morpholino-3-oxopropyl) thio) quinazolin-4 (3*H*) -one (8e):
Yield: 80%; mp: 178-180 °C; IR (cm^{-1}) 2924, 1720, 1605, 1444. ^{1}H-NMR: δ=8.10 (s,1H), 7.65 (1H), 6.50 (3H), 6.30 (3H), 3.55 (4H), 3.40 (6H), 2.75 (2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 170, 165, 162, 148, 135, 132, 130, 129, 128, 126, 122, 120, 119, 64, 57, 26; ESI-MS $[M+H]^+$ *m/z*. 429.

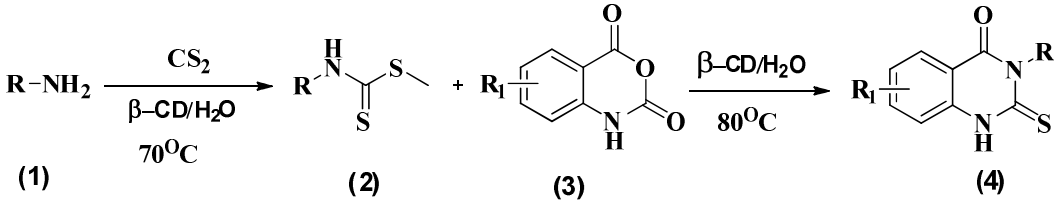
5-Iodo-2- ((3-morpholino-3-oxopropyl) thio)-3-phenylquinazolin-4(3*H*)-one (8f):
Colourless solid, Yield: 90%, mp:126-128 ºC; IR (cm^{-1}): 3221, 1681, 1562, 1362; ^{1}H-NMR: δ= 8.08 (s,1H), 7.70 (1H), 6.20-6.34 (8H), 3.70 (2H), 3.6 (4H), 3.42 (6H), 2.75 (2H); ^{13}C-NMR ($CDCl_3$, 75MHz) δ: 172, 165, 154, 148, 142, 136, 130, 128, 127, 124, 65, 48, 44, 34, 32, 26; ESI-MS $[M+H]^+$ *m/z*. 544.

6-Chloro-2- ((3-morpholino-3-oxypropyl) thio)-3-phenylquinazolin-4(3*H*) -one (8g):
Yellow solid, Yield: 85%; mp: 200-202 °C; IR (cm^{-1}): 2923, 1686, 1556, 1434; ^{1}H-NMR: δ:8.06 (s, 1H), 6.70 (1H), 6.60-6.64 (5H), 3.32-3.54 (9H), 2.80 (2H) 1.36-1.52 (6H); ^{13}C-NMR ($CDCl_3$, 75MHz) δ: 174, 168, 165, 148, 136, 132, 130, 129, 128, 124, 122, 121, 47, 32, 28, 24, 22 ESI-MS $[M+H]^+$ *m/z*.429.

3-Benzyl-2- ((3-morpholino-3-oxopropyl) thio) quinazolin-4(3*H*) -one (8h):
Yield: 90%; white solid, mp: 162-164 °C; IR (cm^{-1}): 2924, 1706,1600, 1521, 1348; ^{1}H-NMR: δ: 8.12 (s, 1H), 8.01(1H), 7.40 (s,1H), 6.84-6.94 (6H), 5.70 (2H), 3.46 (4H), 3.40 (6H), 2.82 (2H); ^{13}C-NMR ($CDCl_3$, 75MHz) δ: 178, 165, 154, 148, 142, 136, 130, 128, 127, 122, 121, 65, 48, 34, 31, 26; ESI-MS $[M+H]^+$ *m/z*. 409.

III. Results and Discussion

The synthetic approach of 2-mercapto quinazolin-4-(3*H*)-one proceeded route presented here by Aniline (**1**) treated with carbon disulphide in the presence of *β*-CD/water obtained methyl phenyl carbamodithioate (**2**). Further the 1*H*- benzo [*d*][1,3]oxazine-2,3-dione (**3**) and methyl phenyl carbamodithioate (2) was presented in *β*-CD aqueous medium leading to form 3-phenyl-2-thioxo-2, 3-dihydroquinazolin-4(1*H*)-one (or) 2-mercapto Quinazolin-4(3*H*)-one (**4**). Spectral data and physical constants confirmed the structure of the product (**4**).



Herein, we focused on *β*-cyclodextrin aqueous media for synthesis of the target molecules in environment benign pathway. The synthetic route to 2-mercapto quinazolin-4(3*H*)-one alkyl/acyl substituted compounds was presented in **schemes 1&2**.

The well-organized synthesis of compounds **6a-b** and **8a-h** was efficiently synthesized in water media. For optimizing the procedure, a reaction was carried out in the water but no yield. For this reason, various mixtures of solvents such as

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toluene, benzene, ethanol and *β*-CD in the presence of water were tested. *β*-CD in the presence of water proved most efficient, leading to the formation of compound 6a in 85% yield. (**Table1, entry5**)

Table 1: Optimization data for synthesis the compound **6a**

Entry	Solvent	mL	Time (h)	Yield (%)
1	H_2O	10	6	-
2	Toluene	10	6	Trace
3	Benzene	10	6	Trace
4	Ethanol	10	6	10
5	*β*-CD/H_2O	10	6	85

The products were confirmed by using ^{1}H-NMR, ^{13}C-NMR, IR and Mass spectral data. The resultant products of Quinazolin-4(3*H*)-one derivatives (**8a-h**) were shown in Table.**2**.

Table 2: Synthesized compounds **8a-h:**

Compound	**R**	**R1**	**X**	**Yield (%)**	**mp (°C)**
8a	p-Cl-Ph	H	CH2	85	146-148
8b	Ph	H	CH2	85	143-145
8c	6-Cl	6-Cl	CH2	80	180-182
8d	-CH2-Ph	H	CH2	85	138-140
8e	p-Cl-Ph	H	O	80	178-180
8f	Ph	5-I	O	90	126-128
8g	Ph	6-Cl	O	85	200-202
8h	-CH2-Ph	H	O	90	162-164

In Vitro Antibacterial Studies:

Quinazolinone derivatives were screened against Gram+*ve* and Gram-*ve* bacteria strains using paper disc diffusion method. The bacterial strains namely *viz. Psued.aeruginosa, Esch. Coli, Baci. Subtilis and Staph. Aureus* was compared reference drugs ciprofloxacin and ofloxacin.

Table 3: MIC Values in (µg/mL):

Compound	*Pseudo. Aeruginosa* *Gram-ve*	*E. Coli* *Gram-ve*	*Baci. Subtilis* *Gram+ve*	*Stap. Aureus* *Gram+ve*
6a	35	>50	30	32
6b	34	32	26	28
8a	>50	42	>50	38
8b	34	32	32	39
8c	42	26	38	42
8d	28	28	26	46
8e	35	34	42	40
8f	29	45	29	36
8g	40	40	36	28
8h	38	39	42	36
Ciprofloxacin	≤21		≤23	
Ofloxacin		≤22		≤20

All Quinazolinone derivatives exhibited excellent antibacterial activity against Gram-*ve* and Gram+*ve* bacteria.

IV. CONCLUSION

In summary, we have synthesized a series of substituted Quinazolinone derivatives (**6a, 6b &8a-8h**) according to green protocol of biomimetic synthetic approach using *β*-CD/H_2O resulted products were excellent yields. Antibacterial activity of successive products examined against various bacterial strain results shown significant activity. We predicted that *β*-cyclodextrin in aqueous media is mild and green synthetic protocol organic transformations in future.

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