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Synthesis of some new thioxoquinazolinone derivatives and a study on their anticonvulsant and antimicrobial activities

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Abstract. – OBJECTIVE: A series of ten novel derivatives of 3-substituted-2-thioxoquinazolin-4(3H)-ones have been synthesized from anthranilic acid via Mannich reaction with various secondary amines in presence of formaldehyde in ice cold condition.

MATERIALS AND METHODS: The structure of these compounds have been elucidated by spectral (FTIR, 1H-NMR and mass) analysis. The titled compounds were evaluated for antimicrobial and anticonvulsant activities. Antimicrobial activities were determined by cup plate method and MIC values using the micro dilution broth method against two Gram positive bacteria *Staphylococcus aureus* and *Streptococcus aureus*, two Gram negative bacteria *Escherichia coli* and *Proteus vulgaris* and against two fungi *Candida albicans* and *Aspergillus niger*. Amikacin and fluconazole were used as standard antibacterial and antifungal agents in the concentration of 10 µg/disc 20 µg/disc respectively.

RESULTS AND CONCLUSIONS: Amongst the compounds tested, compound 2-(2,3-dimethylphenyl) (3-(4-ethoxyphenyl)-4-oxo-2-thioxo-3,4-dihydroquinazolin-1-2H)-1ylmethyl amino)benzoic acid (PTQ-03) and 2-((2,3-dimethylphenyl)((3-(4-ethoxyphenyl)-4-oxo-2-thioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl)amino)benzoic acid (ETQ-03) showed broad spectrum of activity against all the tested Gram positive bacteria, Gram negative bacteria and the fungi. Anti-convulsant activity of the compounds was evaluated by maximal electro shock (MES) convulsion method. The compounds sodium 2-(2-((2,6-Dichlorophenyl)(3-(4-oxo-2-thioxo-3,4-dihydroquinazolin-1(2H)-yl)methyl)amino) phenyl acetate (PTQ-04) and N-(4-Hydroxyphenyl)-N-((3-naphthalen-2-yl)-4-oxo-2-thioxo-3,4-dihydorquinazolin-1(2H)-yl-methyl)acetamide (NTQ-01) showed potent anticonvulsant activity.

Key Words:
Thioxoquinazolinone, Drug likeness, Antibacterial, Antifungal, Anti-convulsant.

Introduction

Quinazoline and quinazolinone derivatives have continued to attract a widespread interest for a long time due to their diverse pharmacological activities like anti-parkinsonism[1], anticonvulsant[2,3], hypoglycemic[4], anti-HIV[5], antimicrobial[6-11], anticancer[12,13] and analgesic[14] activity. Literature survey revealed that the presence of substituted aromatic ring at position 3 and methyl or thiol group at position 2 are essential for the anticonvulsant[15,16] and antimicrobial activities[17]. Based on this fact, more than hundreds of 2-methyl-3-*O*-tolyl-4(3*H*)-quinazolinone and its analogues have been synthesized and tested for central nervous system depression and anticonvulsant activities[18-21]. Hence, we have undertaken the synthesis, characterization, antimicrobial and anticonvulsant evaluation of medicinally important and promising pharmacophore, 4(3*H*)-quinazolinone ring system for our study.

Materials and Methods

Melting points were determined in open capillaries in the electrical melting point apparatus and are uncorrected. Purity of the compounds was checked on silica gel coated Merck-TLC plates using water, chloroform, acetone and benzene as mobile phase. The structure of the synthesized compounds was elucidated by FT-IR (Shizamadu-8400 series, Shizamadu Scientific Instruments, Nakagyo-ku, Kyoto, Japan) in KBr disc, ^{1}H-NMR (Brucker AMX-400 MHz, Brucker Biospin International, Ag, Aegeristrasse, Switzerland) in dimethylsulfoxide-d_6 (DMSO-d_6) and mass spectra using Jeol JMS-DX 303 double focusing mass spectrophotometer (Jeol Ltd, Akishima, Tokyo, Japan). The agar medium and

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potato-dextrose agar (PDA) medium were purchased from Hi-Media Laboratories Ltd., Mumbai, India.

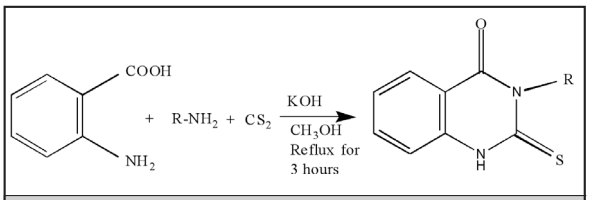
Step-I: Synthesis of 3-substituted Thioxoquinazolin-4(3H) One[22-23]

A mixture of carbon disulfide (30 mmoles) and the appropriate aromatic amines (12 mmoles) was added drop wise to the refluxed mixture of anthranilic acid (10 mmoles) and potassium hydroxide (12 mmoles) in methanol (10 ml). The mixture was heated under reflux for 3 h then the solid produced was filtered, washed with methanol and dried. The solid was dissolved in potassium hydroxide solution (10%, 10 ml), filtered, and then concentrated hydrochloric acid was added to the filtrate. The white precipitate obtained was filtered, washed with water and dried. The crude product obtained was recrystallised from absolute alcohol.

Step II: Synthesis of Thioxoquinazolinone Derivatives by Mannich Reaction

Various 3-substituted-2-thioxoquinazolin-4-(3*H*) ones (0.08 mole) prepared in step 1 was dissolved in methanol in a beaker under ice cold condition. Then 4-hydroxy acetanilide, 4-ethoxy acetanilide, N (2, 3-xylyl) anthranilic acid, sodium [*O*-(2,6-dichloro anilino) phenyl] acetate (0.08 mole) was added separately in small quantities with constant stirring. A measured quantity of formaldehyde solution (0.08 mole) was added, slowly with constant stirring for 4 h. The contents of the beaker were kept over night in a freezer. The crystallized product was filtered, dried and recrystallized from methanol. Characterization data of the synthesized compounds was recorded in Table I.

Step I. Synthesis of 3-substituted-2-thioxoquinazolin-4-(3H)ones.



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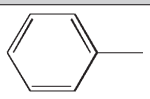
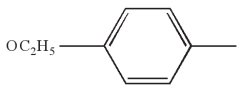
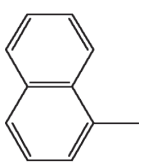
PTQ	
ETQ	
NTQ	

Acute Toxicity Studies

Miller and Tainter[24] method was adopted for the determination of LD_{50} value of the synthesized compounds. Albino mice of either sex (20-30 g) were used for this study. The animals were divided into 15 groups of 6 mice each. The titled compounds were injected intraperitoneally and the mice were observed for 24 h for death due to acute toxicity. LD_{50} values were found to be 200 mg/kg. The doses of the test compounds were then fixed on the basis of their acute toxicity as 20 mg/kg for evaluation of anticonvulsant activity. The animal use protocol has been approved by local Ethical Committee.

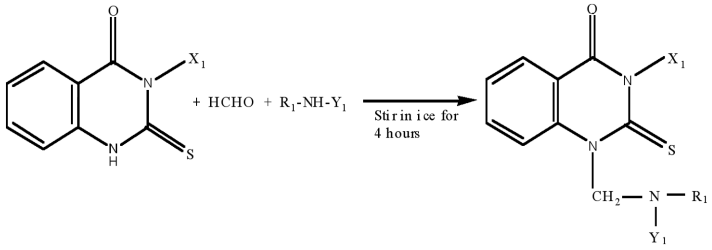
Drug Likeness Properties of Synthesized Compounds[25]

The log P values of the test compounds were calculated by the methodology developed by molinspiration software programme as a sum of fragment based contribution and correction factor. Drug likeness is defined as a complex balance of various molecular properties and structural features, which determines whether the particular molecule is a drug or non-drug. These properties are mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecular characteristics, molecular size, flexibility and presence of various pharmacophoric features which influences the behaviour of molecule in a living organism including characteristics such as transport, affinity to proteins, reactivity, toxicity, metabolic stability and many others. The prediction of molecular and drug like properties was based on the description of "Rule of 5" and the details are recorded in Table II.

Antibacterial Activity

The newly synthesized compounds were screened for their antibacterial activity against two Gram positive bacteria viz. *Staphylococcus aureus*, *Streptococcus aureus* and two Gram negative bacteria *Escherichia coli* and *Proteus vulgaris*

Step II. Synthesis of thioxoquinazolinone derivatives.



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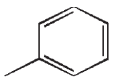
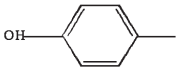
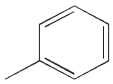
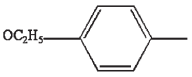
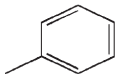
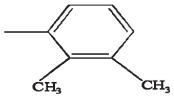
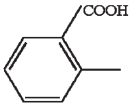
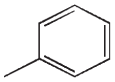
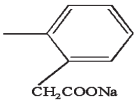
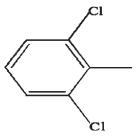
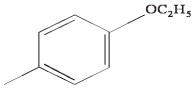
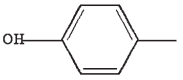
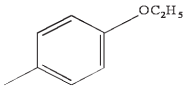
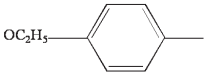
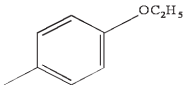
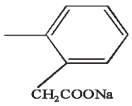
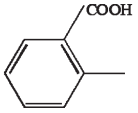
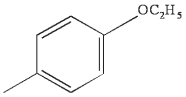
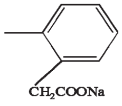
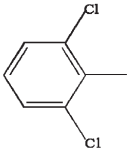
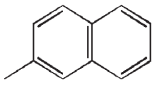
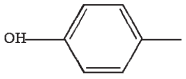
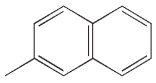
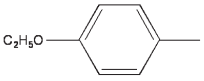
PTQ-01		-$COCH_3$	
PTQ-02		-$COCH_3$	
PTQ-03			
PTQ-04			
ETQ-01		-$COCH_3$	
ETQ-02		-$COCH_3$	
ETQ-03			
ETQ-04			
NTQ-01		-$COCH_3$	
NTQ-02		-$COCH_3$	

Table I. Characterisation data of the synthesized compounds.

Comp code	Molecular formula	Mol. weight	% Yield	Appearance	Melting point (°C)	IR cm^{-1} (KBr disc)	^{1}HNMR (DMSO-6)	MS m/z
PTQ	$C_{14}H_{10}N_2OS$	254.3	84.09	Solid	248-252	–	–	–
PTQ-01	$C_{23}H_{19}N_3O_3S$	417.4	66.81	Solid (crystals)	210-213	2886 (CH_2Str), 1656 (C=OStr), 1324 (Ar-OH), 1170 (C=SStr), 684 (Ar-region)	1.9 (s, 3H, CH_3), 3.1 (s, 2H, CH_2), 5.0 (s, 1H, OH) 6.7 (m,13H,ArH),	418 $[M+1]^+$, 417 $[M]^+$
PTQ-02	$C_{25}H_{23}N_3O_3S$	445.5	70.59	Solid (crystals)	100-105	2927 (CH_2Str), 1660 (C=OStr), 1446 (CH_3) 1110 (-C-O-C), 1172 (C=SStr),	1.9 (q, 3H, CH_3), 2.5 (s, 2H, CH_2) 3.8 (q, 2H, O-CH_2) 7.27 (m,13H, Ar H),	446 $[M+1]^+$ 445 $[M]^+$
PTQ-03	$C_{30}H_{25}N_3O_3S$	507.6	64.65	Solid	222-224	2915 (OH), 1658 (C=O Str), 1440 (-CH_3), 1336 (Ar3oNH) 1197 (C=SStr), 694 (Ar-region)	2.3 (s, 6H, (CH_3) 2) 2.9 (s, 2H, CH_2) 6.7 (m, 16H, ArH) 12.5 (s, 1H, COOH)	–
PTQ-04	$C_{29}H_{20}Cl_2N_3NaO_3S$	584.5	51.02	Solid (amorphous)	160-165	2886 (CH_2-Str) 1567 (COO-) 1195 (C=SStr), 763 (C-Cl),	–	–
ETQ	$C_{16}H_{14}N_2OS$	298.4	62.20	Solid	262-265	–	–	–
ETQ-01	$C_0H_{23}N_3O_4S$	461.5	69.00	Solid (crystals)	180-184	2927 (CH_2Str), 1324 (Ar-OH), 1170 (C=SStr), 1106 (COC) 684 (Ar-region)	2.7 (s, 2H, CH_2), 2.0 (s, 3H, $COCH_3$), 5.0 (s, 1H, OH) 6.7 (m, 8H, ArH),	462 $[M+1]^+$, 461$[M]^+$
ETQ-02	$C_{27}H_{27}N_3O_4S$	489.6	61.03	Solid (crystals)	110-115	2927 (-CH_2Str), 1658 (C=OStr) 1448 (-CH_3), 1174 (C=S Str	1.6 (q, 3H,CH_3) 2.8 (t, 2H, CH_2) 6.7 (m, 8H, ArH)	490 $[M+1]^+$, 489 $[M]^+$
ETQ-03	$C_{32}H_{29}N_3O_4S$	551.7	48.54	Solid	162-168	2566 (OH), 1652 (C=OStr) 1446 (-CH_3), 1159 (C=SStr), 1095 (-COC-)	–	–

Continued page

Table I (***Continued***). Characterisation data of the synthesized compounds.

Comp code	Molecular formula	Mol. weight	% Yield	Appearance	Melting point (°C)	IR cm^{-1} (KBr disc)	^{1}HNMR (DMSO-6)	MS m/z
ETQ-04	$C_{31}H_{24}Cl_2N_3NaO_4S$	628.5	51.77	Solid (amorp)	240-245	1567.84 (COO-), 1197.58 (C=S Str), 1087.66 (-C-O-C-), 748.25 (C-Cl),	1.9 (q, 3H, CH_3) 2.7 (s, 2H, CH_2), 6.9 (m,8H,ArH),	
NTQ	$C_{18}H_{12}N_2OS$	304.4	54.96	Solid	230-233	–	–	–
NTQ-1	$C_{27}H_{21}N_3O_3S$	467.5	61.98	Solid (crystals)	140-145	2879 (CH_2 Str) 1658 (C=O), 1440 CH_3 Str 1324 (Ar-OH), 1174 (C=S Str),	–	
NTQ-2	C29H25N3O3S	495.7	57.62	Solid (crystals)	180-185	2927 (-CH_2 Str), 1660 (C=OStr) 1446 (-CH_3) 1172 (C=SStr), 1110 (-C-O-C), 646 (Ar-region)	8 (s,3H,CH_3), 1. 2.7 (s,2H, CH_2) 3.8 (q,2H, CH_2-CH_3) 7.3 (m, 5H,ArH)	496 [M+1]+ 495 $[M]^+$

Table II. Drug likeness properties of the titled compounds.

Compd code	SMILES notation	logP	TPSA	Natoms	nrotp	nON	nOHNH
PTQ	O=c2c1ccccc1[nH]c(=S)n2c3ccccc3	2.627	37.796	18	1	3	1
PTQ-01	CC(=O)N(Cn3c(=S)n(c1ccccc1)c(=O)c2ccccc23)c4ccc(O)cc4	3.936	67.476	30	4	6	1
PTQ-02	CCC(=O)c4ccc(N(Cn3c(=S)n(c1ccccc1)c(=O)c2ccccc23)C(C)=O)cc4	4.605	64.319	33	6	6	0
PTQ-03	Cc5cccc(N(Cn3c(=S)n(c1ccccc1)c(=O)c2ccccc23)c4ccccc4C(=O)O)c5C	5.765	67.476	37	6	6	1
PTQ-04	O=C[(ONa)]Cc1ccccc1N(cn5c(=s)n(c3ccc2ccccc2c3)c(=o)cccc45)c6c(cl)ccccc6cl	5.942	67.476	38	7	5	1
ETQ	CCOc3ccc(n2c(=S)[nH]c1ccccc1c2=O)cc3	2.976	47.030	21	3	4	1
ETQ-01	CCOc4ccc(n3c(=O)c1ccccc1n(CN(C(C)=O)c2ccc(O)cc2)c3=S)cc4	4.285	76.710	33	6	7	1
ETQ-02	CCOc4ccc(N(Cn3c(=S)n(c1ccc(OCC)cc1)c(=O)c2ccccc23)C(C)=O)cc4	5.018	65.716	35	8	7	0
ETQ-03	CCOc5ccc(n4c(=O)c1ccccc1n(CN(c2ccc(C(=O)O)cc2)c3cccc(C)c3C)c4=S)cc5	6.114	76.710	40	8	7	1
ETQ-04	Ccoc5ccc(n4c(=o)clccccc1n(cN(c2ccccc2cc(=O)[oNa])c3c(cl)cccc3cl)c4=s)cc5	6.291	76.710	41	9	6	1
NTQ	O=c2c1ccccc1[nH]c(=S)n2c4ccc3ccccc3c4	3.917	37.796	22	1	3	1
NTQ-01	CC(=O)N(Cn4c(=S)n(c2ccc1ccccc1c2)c(=O)c3ccccc34)c5ccc(O)cc5	5.226	67.476	34	4	6	1
NTQ-02	CCOc5ccc(N(Cn4c(=S)n(c2ccc1ccccc1c2)c(=O)c3ccccc34)C(C)=O)cc5	5.959	56.482	36	6	6	0

TPSA-Total polar surface area; nrotb-number of rotatable bonds; nON-number of H-bond acceptors; and nOHNH- number of H-bond donors.

by using cup plate method[26]. Discs measuring 6.25 mm in diameter were punched from Whatman No.1 filter paper. The synthesized compounds were dissolved in DMSO to get a final concentration of 1000 µg/mL, where 20 µg/disc of each compound was used for the study. A reference standard for both Gram positive and Gram negative bacteria was made by dissolving accurately weighed quantity of amikacin (10 µg/disc) in DMSO. The incubation was carried out at 37 ± 0.1ºC for 24 h. All the experiments were carried out in triplicate. Simultaneously, controls were maintained by employing 0.1 mL of DMSO which did not reveal any zone of inhibition. Zones of inhibition produced by each compound were measured in mm and the results of antibacterial studies are given in Table III.

Antifungal Activity

Antifungal activity of the titles compounds were done using PDA medium by cup plate method[27] against *Candida albicans* and *Aspergillus niger*. The synthesized compounds were dissolved in DMSO to get a final concentration of 1000 µg/mL, where 20 µg/disc of each compound was used for the study. A reference drug fluconazole (20 µg/mL) and DMSO as control was used for the study. The experiments were performed in triplicate in order to minimize the errors. Zone of inhibition produced by each compound was measured in mm and the results of antifungal studies are given in Table III.

Determination of MIC

MIC, which is the lowest concentration of a compound that completely inhibits microbial growth, was determined by a standard broth dilution technique[27] adapted from the CLSI. For determining MIC for both antibacterial and antifungal activity, the synthesized compounds were dissolved in DMSO to get 100, 50, 25, 12.5, 6.25 *µg*/ml concentrations. Two Gram-positive bacteria, *Streptococcus aureus* ATCC 10832, *Staphylococcus aureus* ATCC 25923, 2 Gram-negative bacteria *Escherichia coli* ATCC 25922, *Proteus vulgaris* ATCC 13315 and 2 fungi and fungi *Candida albicans* 10231 and *Aspergillus niger* 16404 were used for the study.

Bacterial cultures were obtained in Mueller-Hinton broth (Difco) (Sifin Institute for Immunology Products and Culture Media, Berlin, Germany) for all the bacterial strains after 24 h of incubation at 37 ± 0.1°C. The fungi were propagated in Sabouraud dextrose broth (Difco)

Table III. Antimicrobial evaluation of the titled Compounds.

Compound	Zone of inhibition in mm					
	Streptococcus aureus	*Staphylococcus aureus*	*Escherichia Coli*	*Proteus vulgaris*	*Candida albicans*	*Aspergillus niger*
Control	00	00	00	00	00	00
Amikacin	19	14	15	14	–	–
Fluconazole	–	–	–	–	14	14
PTQ-01	06	09	09	7	09	09
PTQ-02	08	08	07	08	08	07
PTQ-03	14	10	11	09	10	11
PTQ-04	11	06	08	05	06	08
ETQ-01	06	11	10	12	11	10
ETQ-02	07	07	08	11	07	08
ETQ-03	14	12	09	12	12	09
ETQ-04	12	10	08	08	10	08
NTQ-01	05	11	10	11	11	10
NTQ-02	07	08	09	07	08	09

*Control: Dimethylsulphoxide.

after incubation for 24 h at 25 ± 0.1°C. Testing was carried out in Mueller–Hinton broth and Sabouraud dextrose broth at pH 7.4 for bacteria and fungi, respectively. Test compounds were dissolved in DMSO at an initial concentration of 100 µg/ml and then serially diluted in culture medium to 6.25 µg/ml. A set of tubes containing only inoculated broth was kept as control. Antibacterial activity was determined after incubation for 24 h at 37°C for bacteria and after incubation for 48 h at 25°C for the fungi.

Evaluation of Anti-Convulsant Activity

Anti-convulsant activity was carried out by using maximal electro shock (MES) induced convulsion method[28]. Albino mice of either sex (25-30 g) were used for the study and divided into 11 groups of 6 mice each. They were given electrical shock through corneal electrodes of 150 mA for 0.2 sec by using electro convulsiometer. Group I were treated with 0.5% v/v tween 80 suspension and served as a control. Group II were treated with phenytoin (20 mg/kg) served as standard. Group III-XI were treated with newly synthesized PTQ-01, PTQ-02, PTQ-03, PTQ-04, ETQ-01, ETQ-02, ETQ-03, NTQ-01 and NTQ-02 compounds (20 mg/kg) respectively. After 30 min seizure induction onset time of tonic flexion, extension and clonic phase were noted. The protective index was observed as reduction time of tonic extensor phase and all the data was observed as reduction time of tonic extensor phase. The animal use protocol has been reviewed and approved by the Institutional Ethical Committee.

Statistical Analysis

All the data were expressed as mean ± SEM. The statistical analysis was performed using Students "*t*" test. A p-value of 0.05 was set as the critical limit of significance.

Results

The synthetic route of thioxoquinazolinones series was presented in the Scheme 1 and 2. The prediction of molecular and drug like properties was based on the description of "Rule of 5" given by Lipinski et al[29]. The rule states that most "drug like" molecules have log P ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, number of hydrogen donors = 5. The rule is called "Rule of 5" because the border values are 5, 5 × 100, 5 × 2 and 5. Based on the above calculation, it was found that the compounds PTQ-01, PTQ-02, ETQ-01 have drug-likeness property.

The synthesized compounds were subjected to antimicrobial screening by cup plate method and broth dilution method. The compounds 2-((2,3-dimethylphenyl)((4-oxo-3-phenyl-2-thioxo-3,4-dihydroquinazolin-1(2*H*)-yl)methyl)amino) benzoic acid (PTQ-03) and 2-((2,3-dimethylphenyl)((3-(4-ethoxyphenyl)-4-

oxo-2-thioxo-3,4-dihydroquinazolin-1(2*H*)-yl) methyl)amino)benzoic acid (ETQ-03) showed broad spectrum of activity against all the tested Gram positive bacteria, Gram negative bacteria and the fungi. The compounds (PTQ-03 and ETQ-03) showed significant activity against Gram positive bacteria *Staphylococcus aureus*.

Minimum inhibitory concentration (MIC) values of synthesized compounds against various organisms are tabulated in Table IV. Titled compounds were graded as highly active with MIC >6.25 to 12.5 µg/ml, moderately active with MIC value 25-50 µg/ml, poorly active with MIC value 50-100 µg /ml. The compound 2-((2,3-dimethylphenyl)((3-(4-ethoxyphenyl)-4-oxo-2- thioxo-3,4-dihydroquinazolin-1(2*H*)-yl) methyl)amino) benzoic acid (ETQ-03) was found to be highly active (6.25 µg/ml) against all the tested microorganism, except *Escherichia coli* and *Aspergillus niger* tested by broth dilution method. The other compounds showed moderate activity with MIC value is an range of > 25 to 100 µg/ml for both bacteria and fungi Sodium 2-(2-((2,6-dichlorophenyl)(4-oxo-3-phenyl-2-thioxo-3,4-dihydroquinazolin-1(2*H*)-yl) methyl) amino)phenyl)acetate (PTQ-04), N-(4-hydroxyphenyl)-N-((3-(naphthalene-2-yl)-4-oxo-2-thioxo-3,4-dihydroquinazolin-1(2*H*)-yl)methyl)acetamide (NTQ-01) and N-(4-ethoxyphenyl)-N-((3-naphthalen-2-yl)-4-oxo-2-thioxo-3,4-dihydroquinazolin-1(2*H*)-yl) methyl)acetamide.

NTQ-02 showed significant anticonvulsant activity and compound PTQ-01 showed moderate activity, compared to that of standard drug, phenytoin at a dose of 20 mg/kg. The anticonvulsant activity of the tested compounds could be arranged in descending order as follows: NTQ-01 > PTQ-04 > NTQ-02 > PTQ-01 > PTQ-02 > NTQ-01 > ETQ-01 > PTQ-03 ETQ-03 > ETQ-02.

Discussion

A series of ten novel derivatives of 3-substituted-2-thioxoquinazolin-4(3*H*)-ones have been synthesized from anthranilic acid via Mannich reaction with various secondary amines in presence of formaldehyde. The structures of the synthesized compounds were established through spectroscopic (IR, 1H-NMR and mass) data. The IR spectra of PTQ, ETQ and NTQ showed the presence of NH band (3309 cm^{-1}), C=O band (1660 cm^{-1}), C=S band (1170 cm^{-1}), while the ^{1}H-NMR spectra showed the signals aromatic protons and NH protons (proton signals that disappeared on deuterium exchange) for PTQ and NTQ. ETQ showed signals for methyl and methylene protons. Disappearance of NH absorption bands both in IR and ^{1}H-NMR spectra confirms that the substitution has taken place in N-1position of the titled compounds. In addition to the C=O band (1660 cm^{-1}), C=S band (1170 cm^{-1}), PTQ-01, ETQ-01 and NTQ-01 showed IR absorption bands for Ar-OH, PTQ-03 and ETQ-03 showed IR absorption bands for COOH, PTQ-04 and ETQ-04 showed IR absorption bands for C-Cl. In addition to multiplet signals for Ar-H from d 6.7 to 8.2, PTQ-01, ETQ-01 and NTQ-01 showed ^{1}H-NMR absorption singlet signals at d 2 for CO$\underline{CH_3}$ and d 5 for protons of Ar-$\underline{OH}$. Similarly the proton signals of the synthesized com-

Table IV. Minimal Inhibition Concentration of titled compounds*.

Compound code	*Streptococcus aureus*	*Staphylococcus aureus*	*Escherichia Coli*	*Proteus vulgaris*	*Candida albicans*	*Aspergillus niger*
Standard	6.25	6.25	6.25	6.25	6.25	6.25
PTQ-01	< 100	25	25	50	25	25
PTQ-02	25	25	25	50	50	50
PTQ-03	6.25	12.5	12.5	25	12.5	12.5
PTQ-04	12.5	< 100	25	< 100	< 100	25
ETQ-01	< 100	12.5	12.5	6.25	6.25	12.5
ETQ-02	50	50	25	12.5	50	25
ETQ-03	6.25	6.25	25	6.25	6.25	25
ETQ-04	6.25	12.5	25	25	12.5	50
NTQ-01	< 100	12.5	12.5	25	12.5	12.5
NTQ-02	50	25	25	50	25	25

*Average of three determinations: All the MIC values are in µg/ml.

pounds were in correlation with the expected structures. The mass spectrum of the titled compounds exhibited the molecular ion peak (M+) for their respective molecular weights.

The broad spectrum of activity of PTQ-03 and ETQ-03 against all the tested Gram positive bacteria, Gram negative bacteria and the fungi may be due to the aromatic carboxylic acid moiety. The maximum activity against Gram positive bacteria, Gram negative bacteria and fungi indicated for ETQ-03 (MIC = 6.25 μg/ml) and ETQ-03 (MIC = 12.5 μg/ml) suggests that the electron-withdrawing COOH group plays a crucial role in enhancing the observed activity.

The newly synthesized compounds were screened for their anticonvulsant activity by the Maximal Electroshock (MES) induced seizures method, wherein electroshocks were applied via corneal electrodes using phenytoin as a reference drug. MES test was adopted for the study as compounds rendering protection in this test may prove to be useful in treating generalized tonic-clonic and complex partial seizures.

The compounds PTQ-01, PTQ-04 and NTQ-01 showed significant ($p < 0.05$ and $p < 0.001$) protection against MES-induced convulsion since electron withdrawing group at different positions of aryl ring are being substituted, which demonstrates potent anticonvulsant activity (Table V). This observation suggests that introduction of $COCH_3$ group, 2',4'-Cl group and $COCH_3$ group in the respective structures produced superior anticonvulsant activity. This is further evidenced by optimum logP values (Table II) in PTQ-01, PTQ-04 and NTQ-01 that ensured lipophilicity required by the compounds. Although the drug levels in cerebrospinal fluid (CSF) or in brain were not measured, higher logP values for the potent molecules suggest that there is a correlation between anticonvulsant activity and lipophilicity.

Conclusions

In this study, a new series of thioxoquinazolinones were synthesized and their anticonvulsant and antimicrobial activity was determined. Among the newly synthesized derivatives compound 2-((2,3-dimethylphenyl)((3-(4-ethoxyphenyl)-4-oxo-2- thioxo-3,4-dihydroquinazolin-1(2*H*)-yl) methyl)amino) benzoic acid (ETQ-03) and compound 2-(2,3-dimethylphenyl)(3-(4-ethoxyphenyl)-4-oxo-2-thioxo-3,4-dihydroquinazolin-1-2H)-1ylmethyl amino)benzoic acid (PTQ-03) displayed promising antimicrobial activity. Compound PTQ-04, sodium 2-(2-((2,6-dichlorophenyl)(3-(4-oxo-2-thioxo-3,4-dihydroquinazolin-1(2*H*)-yl)methyl) amino)phenyl acetate displayed promising anticonvulsant activity.

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Table V. Anticonvulsant evaluation of the titled compounds.

S.No.	Treatment	Extensor (sec) (mean ± SEM)	Clonus (sec) (mean ± SEM)	Stupor (sec) (mean ± SEM)	Mortality
1.	Control	30.67 ± 0.9124	24.67 ± 0.8642	53.74 ± 0.8424	Recovery
2.	Phenytoin	12.14 ± 0.5032**	13.43 ± 0.4482	30.24 ± 0.6842	Recovery
3.	PTQ-01	14.78 ± 0.7774**	19.17 ± 0.8812	33.47 ± 0.7943	Recovery
4.	PTQ-02	19.47 ± 0.8374**	21.67 ± 0.6212	33.24 ± 0.8946	Recovery
5.	PTQ-03	22.14 ± 0.7124**	22.84 ± 0.5964	38.54 ± 0.7814	Recovery
6.	PTQ-04	14.19 ± 0.6218**	17.77 ± 0.5212	35.50 ± 0.8624	Recovery
7.	ETQ-01	21.76 ± 0.8114	20.43 ± 0.7621	34.74 ± 0.9164	Recovery
8.	ETQ-02	23.74 ± 0.9132*	19.03 ± 0.5827	43.43 ± 0.576	Recovery
9.	ETQ-03	23.12 ± 0.4124	22.43 ± 0.7246	51.74 ± 0.9164	Recovery
10.	NTQ-01	13.45 ± 0.9123**	19.74 ± 0.5247	41.17 ± 0.7129	Recovery
11.	NTQ-02	14.24 ± 0.9097*	22.14 ± 0.1241	41.44 ± 0.8648	Recovery

#Dose of test compounds and standard administered is 20 mg/kg. **$p < 0.001$ indicates the highly significant difference compared with control. *$p < 0.05$ indicates the significant difference compared with control.

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