Synthesis and QSAR Study of (4-Oxo-3-aryl-3,4-dihydro-quinazolin-2-ylsulfanyl)-propionic Acid arylidene/aryl-ethylidene-hydrazides via Microwave Assisted Solvent Free Reactions

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Abstract: In the present work, *s*-alkylated derivatives of thio-quinazolinone were obtained using Methyl 2-chloro propionate via a solvent-free microwave-assisted method. The alkylated thio quinazolinones were further sequentially condensed with hydrazine hydrate and different aromatic aldehydes to get the hydrazides, which were studied for QSAR. The synthesized compounds were subjected to a prediction of biological activities. A software application (PASS) was used for this purpose. The relationship between structure and different biological activities was studied and the different derivatives were recommended for the screening of some specific activities like anti-tuberculosic, anti-mycobacterial & HDL cholesterol increasing activities.

Keywords: Quinazolinone, Antituberculosic, Anti-mycobacterial, HDL cholesterol increasing, QSAR

Introduction

In recent years the use of microwave irradiation in organic reactions is rapidly increasing because of the short reaction time, operational simplicity and formation of clean reaction products. Avoiding use of organic solvent during the reactions in organic synthesis leads to a clean, efficient and economical technology (green chemistry). It has been commonly employed as thermal energy source in various organic reactions¹. The use of domestic microwave oven in this regard is now a well-established procedure in MORE² (microwave induced organic reaction enhancement) chemistry. It has been reported that the rate of variety of organic reactions such as Diels-Alder³, ene⁴, Claisen reaction⁵, oxidation⁶, reduction⁷, diacetylation⁸, deacetylation⁹, deoxygenation¹⁰, esterification¹¹, hydrolysis of ester¹², Doebner condensation¹³, Knoevenagel condensation¹⁴ could be enhanced by microwave irradiation. Several workers have reported the alkylation of *N*-containing heterocycles. In this regard microwave (MW) activation have been successfully applied in the synthesis of such derivatives¹⁵⁻¹⁷.

Quinazoline derivatives are of special importance because of their versatile biological & pharmacological activities¹⁸⁻²⁰, especially anti-inflammatory²¹⁻²³, anti-convulsant²⁴, hypnotic²⁵, anthelmintic²⁶, hypotensive²⁷, antibacterial²⁸ agents *etc.* In the present work, *s*-alkylated derivatives of thio-quinazolinone were obtained using Methyl 2-chloro propionate via a solvent-free microwave-assisted method. The alkylated thio quinazolinones were further sequentially condensed with hydrazine hydrate and different aromatic aldehydes to get the hydrazides, which were studied for QSAR. The synthesized compounds were subjected to a prediction of biological activities. A software application (PASS) was used for this purpose. The relationship between structure and different biological activities was studied and the different derivatives were recommended for the screening of some specific activities.

Experimental Section

All mps. were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on Shimadzu IR-437 spectrophotometer and PMR spectra in CDCl₃ and DMSO-d₆ on Perkin-Elmer R-32 spectrometer using TMS as an internal standard. The purity of the compounds was checked by TLC. Microwave irradiation was carried out in the domestic microwave oven by SHARP.

2-(4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)- propionic acid methyl ester (II-a)

The mixture of Compound I-a 0.67 g (2.5 mmol), methyl 2-chloropropionate 0.306 g (2.5mmol) in of DMF (5 mL) to which powdered NaOH (0.5 g) was smoothly mixed and placed inside a Pyrex-glass open vessel .The mixture was irradiated with microwaves (900 W /2450 MHz frequency) for the specified time on 50% power using a domestic microwave oven ‘ Sharp R-758B’. When the irradiation was stopped, the final temperature was measured by introducing a glass thermometer into the homogenized reaction mixture. To this mixture then 2N HCl (10 mL) was added and the separated solid was filtered, conveniently dried and recrystallized from aq. Ethanol to get 0.761 g of II-a. Yield 86%, M.P.145°C, Mol. Wt.354, Molecular formula C₁₉H₁₈N₂O₃S, Elemental analysis C, 64.5 (64.41%); H, 5.0 (5.08%); N, 7.8 (7.91%). IR(KBr): $\nu_{\max}$, 1755(C=O),1710(cyclicC=O), 1620(C=N), 1060cm⁻¹(-O-), PMR (DMSO-d₆): δ , 1.4(3H,d J=7Hz. ,CH₃),2.35(3H,s,Ar-CH₃), 3.75(3H, s,OCH₃), 4.3(2H,q J=7Hz.,CH), 7.2-8.2(8H,m,Ar-H) ppm.

Similarly, the other compounds II-(b-g) were prepared and their purity was checked by TLC and the structures confirmed on the basis of IR and PMR spectral and elemental analysis data.

2-(4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-propionic acid hydrazide (III-a)

Compound II-a 3.54 g (0.1mol) mixed with 0.1 mols of hydrazine hydrate in methanol 5 mL was refluxed on a steam bath for three hours. The separated solid was filtered and recrystallized from ethanol to get 3.115 g of III-a. Yield 88%, M. P. 188°C. , Molar Mass: 354,Mol. Formula: C₁₈H₁₈N₄O₂S, Elemental Analysis: C, 60.9(61.00%); H, 5.1(5.12%); N, 15.8 (15.81%), IR (KBr): $\nu_{\max}$, 3200-3080(NH-NH₂), 1680(cyclic >C=O), 1660(acyclic>C=O), 1620cm⁻¹(C=N), PMR(DMSO-d₆): δ , 1.55 (3H,d,J=7.5Hz.,CH₃),3.75 (3H, s, Ar-CH₃),4.5(1H, q, J=8.5Hz, CH),-4.8(2H, s, br, exchangeable with D₂O, NH₂), 6.8-8.1(8H,m,Ar-H), 9.45(1H, s, CONH) ppm.

2-(4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-propionic acid(4-methoxy-benzylidene)-hydrazide (IV-a₄)

Mixture of Compound III-a 3.54 g (0.1 mol) and 4-methoxy benzaldehyde 1.36 g (0.1 mol) in DMF (5 mL) to which 2-3 drops of acetic acid were added and the reaction mixture was mixed well and placed inside a Pyrex-glass Erlenmeyer flask loosely corked with cotton. The mixture was irradiated with microwaves (900 W /2450 MHz frequency) for 5 minutes on 50% power using a domestic microwave oven 'Sharp R-758B'. When the irradiation was stopped, the mixture was added to ice-water mixture and the separated solid was filtered, conveniently dried and recrystallized from aq. ethanol to get 3.68 g of IV-a₄. Yield 78%, M.P. 332°C., Molar Mass: 472, Mol. Formula : C₂₆H₂₄N₄O₃S, Elemental analysis: C,66.1(66.08%); H,5.1(5.12%); N,11.8(11.86 %) ,IR (KBr): $\nu_{\max}$, 1720(cyclic amido >C=O), 1680(acyclic >C=O), 1610 cm⁻¹.(C=N), PMR(DMSO-d₆): δ ,1.55(3H,d, J=7.5Hz.,CH₃), 2.9(3H,s,Ar-CH₃), 3.8(3H,s, Ar-OCH₃), 4.5(1H,q, J=7.5Hz.,CH),7.3-8.3(12H,m,Ar-H), 8.5(3H,s,=C-CH),9.6(1H,s,CONH) ppm.

2-(4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl) propionic acid [1-(2-hydroxy-phenyl)-ethylidene]-hydrazide [V-a₁]

The mixture of Compound III-a 3.54 g (0.1 mol) and 1-(2-hydroxy phenyl) acetone 1.36 g (0.1 mol) in DMF (5 mL) to which 2-3 drops of acetic acid were added, placed inside a Pyrex-glass Erlenmeyer flask loosely corked with cotton. The mixture was irradiated with microwaves (900 W /2450 MHz frequency) for 8 minutes on 50% power using a domestic

microwave oven 'Sharp R-758B'. When the irradiation was stopped, the mixture was added to ice-water mixture. The solid separated was filtered, conveniently dried and recrystallized from ethanol to get 4.012 g of V-a₂. Yield 85%, M.P. 354°C., Mol. Wt. 472, Mol. Formula : C₂₆H₂₄N₄O₃S, Elemental analysis: C, 66.0(66.08%); H, 5.10(5.12%); N, 11.9(11.86%) ,IR (KBr): $\nu_{\max}$, 3300-3100(phenolic OH), 1720(cyclic amido), 1680(acyclic >C=O), 1610 cm⁻¹.(C=N), PMR (DMSO-d₆): δ , 1.45(3H,d,J=7.5Hz.,CH₃), 2.1(3H,s,=CCH₃), 2.35(3H,s, Ar-CH₃), 4.3(1H,q, J=7.5Hz.,CH), 7.3-8.3(12H,m,Ar-H), 9.6(1H,s,CONH), 12.5(1H,s,br,OH) ppm.

Results and Discussion

The compounds of the type (4-Oxo-3-aryl -3,4-dihydro-quinazolin-2-ylsulfanyl)-propionic acid (substituted-benzylidene)-hydrazide IV (a-g)(1-6) were studied for the predictions of their probabilities of being active [Pa] and inactive [Pi] for the selected activities such that the Pa>70% .A software application (PASS) was used for this purpose. The relationship between structure and different biological activities was studied. It was found that the 2-methy phenyl quinazolinones are expected to exhibit spectacular HDL Cholesterol Increasing activity, whereas the 3- chloro-phenyl and 4-chlorophenyl quinazolinone condensed with all the three substituted benzaldehydes are expected to exhibit spectacular HDL Cholesterol Increasing activity. Other 4-substituted phenyl derivatives are also expected to exhibit spectacular HDL Cholesterol Increasing activity. Hence these compounds are recommended for the screening of HDL Cholesterol Increasing activity. Similarly the derivatives of quinazolinones condensed with different aromatic ketones were when subjected to PASS, we found only one activity at Pa>70%. The derivatives with R₁=2-Me are expected to exhibit spectacular HDL cholesterol increasing activity. Whereas the derivatives of quinazolinones condensed with 4-methyl substituted benzophenone were found to be more probably active as compared with those substituted with other groups. In the present scheme, unlike the similar acetic acid hydrazide derivatives of the quinazolinones, one cant draw a conclusion about the expected more activity for the quinazolinone derivatives condensed with different aromatic ketones as compared to those with aldehydes. Hence these compounds were recommended for the screening of HDL Cholesterol Increasing activity.

Table 1. Physical and Analytical data of the compounds [II-(a-g)]

Compd	R	MW, min.	Yield, %	M.P. °C	Mol Formula	Elemental Analysis Found		
						Calcd, %		
						C	H	N
II-b	3-Me	3.5	85	165	C ₁₉ H ₁₈ N ₂ O ₃ S	64.35 (64.39)	5.11 (5.12)	7.92 (7.90)
II-c	4-Me	3.5	84	148	C ₁₉ H ₁₈ N ₂ O ₃ S	64.42 (64.39)	5.20 (5.12)	7.91 (7.90)
II-d	3-Cl	3.0	75	138	C ₁₈ H ₁₅ ClN ₂ O ₃ S	57.69 (57.68)	4.00 (4.03)	7.4 (7.47)
II-e	4-Cl	3.0	76	128	C ₁₈ H ₁₅ ClN ₂ O ₃ S	57.59 (57.68)	4.10 (4.03)	7.45 (7.47)
II-f	3-OMe	3.0	79	146	C ₁₉ H ₁₈ N ₂ O ₄ S	61.60 (61.61)	4.89 (4.90)	7.50 (7.56)
II-g	4-OMe	2.5	77	101	C ₁₉ H ₁₈ N ₂ O ₄ S	61.56 (61.61)	4.85 (4.90)	7.53 (7.56)

Table 2. Spectral characteristics of the compounds [II-(b-g)]

Comp	IR $\nu_{\max}$, cm^{-1}	PMR δ , ppm.
II-b	1755(>C=O), 1710(cyclic amido >C=O), 1620 (C=N), 1060(-O-).	1.4(3H,d, J=7.5Hz.,CH ₃), 2.35(3H,s, Ar-CH ₃), 3.75(3H,s, OCH ₃), 4.3(1H,q, J=7.5Hz.,CH), 7.2-8.2(8H,m, Ar-H).
II-c	1760(>C=O), 1680(cyclic amido >C=O), 1620 (C=N), 1060(-O-).	1.55(3H,d,J=7.5Hz.,CH ₃), 2.25(3H,s, Ar-CH ₃), 3.75(3H,s, CH ₃), 4.3(1H,q, J=7.5Hz.,CH), 7.3-8.3(8H,m,Ar-H).
II-d	1740(>C=O), 1690(cyclic amido >C=O), 1625 (>C=N), 1060(-O-), 760(C-Cl).	1.50(3H,d,J=7.5Hz.,CH ₃), 3.75(3H,s, OCH ₃), 4.3(1H,q, J=7.5Hz.,CH), 7.2-8.1(8H,m,Ar-H).
II-e	1750(>C=O), 1700 (cyclic amido >C=O), 1620 (>C=N), 1055(-O-), 760(C-Cl)	1.42(3H,d,J=7.5Hz.,CH ₃), 3.80(3H,s, OCH ₃), 4.4(1H,q, J=7.5Hz.,CH), 7.5-8.3(8H,m, Ar-H),
II-f	1750(>C=O), 1710(cyclic >C=O), 1620(>C=N), 1060(-O-)	1.45(3H,d,J=7.5Hz.,CH ₃), 3.75(3H,s, OCH ₃), 3.8(3H,s,Ar-OCH ₃), 4.4(1H,q, J=7.5Hz.,CH), 7.18-8.1(8H,m,Ar-H),
II-g	1745(>C=O), 1690(cyclic >C=O), 1620(>C=N), 1060(-O-)	1.55(3H,d,J=7.5Hz.,CH ₃), 3.65(3H,s, OCH ₃ ester), 3.75(3H,s,Ar-OCH ₃), 4.45(1H,q, J=7.5Hz.,CH), 6.8-8.15(8H,m,Ar-H),

Table 3. General characteristics and elemental analysis data of the compounds [III-(a-g)]

Comp.	R	Yield, %	M.P. °C	Mol. Formula	Elemental Analysis		
					Found (Calcd) %		
					C	H	N
III-b	3-Me	78	178	C ₁₈ H ₁₈ N ₄ O ₂ S	61.01 (61.00)	5.13 (5.12)	15.80 (15.81)
III-c	4-Me	89	179	C ₁₈ H ₁₈ N ₄ O ₂ S	61.11 (61.00)	5.13 (5.12)	15.78 (15.81)
III-d	3-Cl	85	184	C ₁₇ H ₁₅ ClN ₄ O ₂ S	54.45 (54.47)	4.02 (4.03)	15.00 (14.95)
III-e	4-Cl	74	198	C ₁₇ H ₁₅ ClN ₄ O ₂ S	54.45 (54.47)	4.01 (4.03)	14.90 (14.95)
III-f	3-OMe	86	235	C ₁₈ H ₁₈ N ₄ O ₃ S	58.34 (58.36)	4.91 (4.90)	15.15 (15.12)
III-g	4-OMe	89	244	C ₁₈ H ₁₈ N ₄ O ₃ S	58.33 (58.36)	4.91 (4.90)	15.10 (15.12)

Table 4. Spectral Characteristics of the compounds [III-(b-g)]

Comp.	IR $\nu_{\max}$, cm^{-1}	PMR δ , ppm.
III-b	3200-3080 (-NHNH ₂), 1680(br. cyclic and acyclic >C=O), 1615 (>C=N),	1.55(3H,d, J=7.5Hz.,CH ₃), 3.75(3H,s, Ar-CH ₃), 4.5(1H,q, J=7.5Hz.,CH), 4.8(2H,s, br. exchangeable with D ₂ O,NH ₂), 7.2-8.2(8H,m, Ar-H) 9.45(1H,s, br, CONH).
III-c	3350-3190 (-NHNH ₂), 1685(br. cyclic and acyclic >C=O), 1615 (>C=N),	1.45(3H,d, J=7.5Hz.,CH ₃), 2.25(3H,s, Ar-CH ₃), 4.3(1H,q, J=7.5Hz.,CH), 4.8(2H,s, br. exchangeable with D ₂ O,NH ₂), 7.3-8.3(8H,m, Ar-H), 9.5(1H,s, br, CONH).
III-d	3180-3060 (-NHNH ₂), 1675(br.cyclic and acyclic>C=O), 1620 (>C=N), 760(C-Cl).	1.50(3H,d, J=7.5Hz.,CH ₃), 4.3(1H,q, J=7.5Hz.,CH), 4.9(2H,s, br. exchangeable with D ₂ O,NH ₂), 7.2-8.1(8H,m, Ar-H), 9.8(1H,s, br, CONH).
III-e	3250-3130 (-NHNH ₂), 1685(br.cyclic and acyclic>C=O), 1620 (>C=N), 760(C-Cl)	1.42(3H,d, J=7.5Hz.,CH ₃), 4.4(1H,q, J=7.5Hz.,CH), 4.8(2H,s, br. exchangeable with D ₂ O,NH ₂), 7.5-8.3(8H,m, Ar-H), 9.75(1H,s, br, CONH).
III-f	3300-3180 (-NHNH ₂), 1680(br.cyclic and acyclic>C=O), 1615 (>C=N), 1060(-O-)	1.45(3H,d, J=7.5Hz.,CH ₃), 3.8(3H,s, Ar-OCH ₃), 4.4(1H,q, J=7.5Hz.,CH), 4.95(2H,s,br. exchangeable with D ₂ O,NH ₂), 7.18-8.1(8H,m,Ar-H), 9.65(1H,s,br, CONH).

Table 5. Physical and analytical data of the compounds IV-(a-g)₍₁₋₆₎

IV	R	R'	MW Mins.	Yield %	M.P. °C	Mol. Formula.	Elemental Analysis		
							Found, Calcd, %		
							C	H	N
a ₁	2-Me	H	2.5	85	212	C ₂₅ H ₂₂ N ₄ O ₂ S	62.84	5.00	12.70
							(62.85)	(5.01)	(12.66)
							63.00	4.42	11.76
a ₂	2-Me	2-Cl	2.0	75	252	C ₂₅ H ₂₁ ClN ₄ O ₂ S	(62.95)	(4.44)	(11.75)
							62.98	4.45	11.77
a ₃	2-Me	4-Cl	2.5	85	269	C ₂₅ H ₂₁ ClN ₄ O ₂ S	(62.95)	(4.44)	(11.75)
							66.10	5.10	11.84
a ₄	2-Me	4-Ome 3OMe,	2.5	86	233	C ₂₆ H ₂₄ N ₄ O ₃ S	(66.08)	(5.12)	(11.86)
							63.91	4.96	11.50
a ₅	2-Me	4OH 3,4,5	3.0	84	245	C ₂₆ H ₂₄ N ₄ O ₄ S	(63.92)	(4.95)	(11.47)
							63.12	5.26	10.50
a ₆	2-Me	triOMe	3.0	82	248	C ₂₈ H ₂₈ N ₄ O ₅ S	(63.14)	(5.30)	(10.52)
							62.84	5.00	12.65
b ₁	3-Me	H	3.5	83	287	C ₂₅ H ₂₂ N ₄ O ₂ S	(62.85)	(5.01)	(12.66)
							62.98	4.45	11.74
b ₂	3-Me	2-Cl	3.0	71	289	C ₂₅ H ₂₁ ClN ₄ O ₂ S	(62.95)	(4.44)	(11.75)
							62.95	4.42	11.78
b ₃	3-Me	4-Cl	3.0	72	299	C ₂₅ H ₂₁ ClN ₄ O ₂ S	(62.95)	(4.44)	(11.75)
							66.05	5.11	11.85
b ₄	3-Me	4-Ome 3OMe,	3.5	70	274	C ₂₆ H ₂₄ N ₄ O ₃ S	(66.08)	(5.12)	(11.86)
							63.95	4.96	11.52
b ₅	3-Me	4OH 3,4,5	3.0	77	277	C ₂₆ H ₂₄ N ₄ O ₄ S	(63.92)	(4.95)	(11.47)
							63.15	5.26	10.53
b ₆	3-Me	triOMe	3.0	87	284	C ₂₈ H ₂₈ N ₄ O ₅ S	(63.14)	(5.30)	(10.52)
							62.84	5.00	12.70
c ₁	4-Me	H	2.5	84	285	C ₂₅ H ₂₂ N ₄ O ₂ S	(62.85)	(5.01)	(12.66)
							62.98	4.45	11.76
c ₂	4-Me	2-Cl	2.0	87	289	C ₂₅ H ₂₁ ClN ₄ O ₂ S	(62.95)	(4.44)	(11.75)
							62.95	4.42	11.74
c ₃	4-Me	4-Cl	2.5	85	266	C ₂₅ H ₂₁ ClN ₄ O ₂ S	(62.95)	(4.44)	(11.75)
							66.07	5.11	11.90
c ₄	4-Me	4-Ome 3OMe,	3.0	84	245d	C ₂₆ H ₂₄ N ₄ O ₃ S	(66.08)	(5.12)	(11.86)
							63.95	4.96	11.48
c ₅	4-Me	4OH 3,4,5	3.0	82	259	C ₂₆ H ₂₄ N ₄ O ₄ S	(63.92)	(4.95)	(11.47)
							63.15	5.28	10.53
c ₆	4-Me	triOMe	3.0	81	248	C ₂₈ H ₂₈ N ₄ O ₅ S	(63.14)	(5.30)	(10.52)
							62.25	4.16	12.12
d ₁	3-Cl	H	3.0	81	278	C ₂₄ H ₁₉ ClN ₄ O ₂ S	(62.27)	(4.14)	(12.10)
							58.00	3.68	11.30
d ₂	3-Cl	2-Cl	3.5	83	287	C ₂₄ H ₁₈ Cl ₂ N ₄ O ₂ S	(57.95)	(3.65)	(11.26)
							57.90	3.62	11.25
d ₃	3-Cl	4-Cl	3.5	80	299	C ₂₄ H ₁₈ Cl ₂ N ₄ O ₂ S	(57.95)	(3.65)	(11.26)

Contd....

d ₄	3-Cl	4-Ome	3.0	88	286	C ₂₅ H ₂₁ ClN ₄ O ₃ S	60.90 (60.91)	4.30 (4.29)	11.35 (11.36)
		3OMe,4					59.20	4.15	11.00
d ₅	3-Cl	OH	3.0	84	281	C ₂₅ H ₂₁ ClN ₄ O ₄ S	(59.00)	(4.16)	(11.01)
		3,4,5					58.63	4.55	10.15
d ₆	3-Cl	triOMe	3.0	87	283	C ₂₇ H ₂₅ ClN ₄ O ₅ S	(58.64)	(4.56)	(10.13)

IV	R	R'	MW Mins	Yield %	M.P. °C.	Mol. Formula	Elemental Analysis Found (Calcd) %		
							C	H	N
e ₁	4-Cl	H	3.5	89	274	C ₂₄ H ₁₉ ClN ₄ O ₂ S	62.25 (62.27)	4.16 (4.14)	12.12 (12.10)
e ₂	4-Cl	2-Cl	3.5	88	277	C ₂₄ H ₁₈ Cl ₂ N ₄ O ₂ S	57.96 (57.95)	3.68 (3.65)	11.25 (11.26)
e ₃	4-Cl	4-Cl	3.0	90	263	C ₂₄ H ₁₈ Cl ₂ N ₄ O ₂ S	57.96 (57.95)	3.62 (3.65)	11.25 (11.26)
e ₄	4-Cl	4-Ome	3.5	84	256	C ₂₅ H ₂₁ ClN ₄ O ₃ S	60.90 (60.91)	4.30 (4.29)	11.41 (11.36)
e ₅	4-Cl	3OMe,4 OH	3.5	80	265	C ₂₅ H ₂₁ ClN ₄ O ₄ S	58.96 (59.00)	4.18 (4.16)	11.00 (11.01)
e ₆	4-Cl	3,4,5 triOMe	3.5	80	263	C ₂₇ H ₂₅ ClN ₄ O ₅ S	58.67 (58.64)	4.60 (4.56)	10.20 (10.13)
f ₁	3-OMe	H	3.5	83	269	C ₂₅ H ₂₂ N ₄ O ₃ S	65.50 (65.49)	4.85 (4.84)	12.23 (12.22)
f ₂	3-OMe	2-Cl	3.0	84	298	C ₂₅ H ₂₁ ClN ₄ O ₃ S	60.92 (60.91)	4.32 (4.29)	11.35 (11.36)
f ₃	3-OMe	4-Cl	3.0	83	288	C ₂₅ H ₂₁ ClN ₄ O ₃ S	60.90 (60.91)	4.28 (4.29)	11.34 (11.36)
f ₄	3-OMe	4-Ome	3.0	82	247	C ₂₅ H ₂₁ ClN ₄ O ₃ S	60.90 (60.91)	4.28 (4.29)	11.34 (11.36)
f ₅	3-OMe	3OMe, 4OH	3.5	86	248	C ₂₆ H ₂₄ N ₄ O ₄ S	63.92 (63.92)	4.97 (4.95)	11.45 (11.47)
f ₆	3-OMe	3,4,5 triOMe	3.5	85	302	C ₂₆ H ₂₄ N ₄ O ₅ S	61.88 (61.89)	4.77 (4.79)	11.11 (11.10)
g ₁	3-OMe	H	3.5	85	305	C ₂₈ H ₂₈ N ₄ O ₆ S	61.28 (61.30)	5.16 (5.14)	10.20 (10.21)
g ₂	4-OMe	2-Cl	3.0	87	310	C ₂₅ H ₂₂ N ₄ O ₃ S	65.50 (65.49)	4.85 (4.84)	12.23 (12.22)
g ₃	4-OMe	4-Cl	3.5	88	314	C ₂₅ H ₂₁ ClN ₄ O ₃ S	60.92 (60.91)	4.32 (4.29)	11.35 (11.36)
g ₄	4-OMe	4-Ome	3.0	89	300	C ₂₅ H ₂₁ ClN ₄ O ₃ S	60.90 (60.91)	4.30 (4.29)	11.35 (11.36)
g ₅	4-OMe	3OMe, 4OH	3.5	88	287	C ₂₆ H ₂₄ N ₄ O ₄ S	63.89 (63.92)	4.98 (4.95)	11.49 (11.47)
g ₆	4-OMe	3,4,5 triOMe	3.0	84	278	C ₂₆ H ₂₄ N ₄ O ₅ S	61.90 (61.89)	4.80 (4.79)	11.00 (11.10)

Table 6. Spectral data of compounds from IV-(a-g)₍₁₋₆₎

Comp. No.	IR vmax, cm ⁻¹	PMR δ , ppm.
IV-a ₂	1700(cyclic amido), 1680(acyclic >C=O), 1620(>C=N).	1.35(3H,d,CH ₃), 2.25(3H,s, Ar-CH ₃), 4.3(1H,q,CH), 7.3-8.3(12H,m, Ar-H), 8.5(1H,s,=C-CH), 9.5(1H,s, br, CONH).
IV-a ₄	1700(cyclic amido), 1680(acyclic >C=O), 1620(>C=N), 1600(-O-).	1.35(3H,d,CH ₃), 2.25(3H,s, Ar-CH ₃), 3.80(3H,s, Ar-OCH ₃), 4.3(1H,q,CH), 7.3-8.3(12H,m, Ar-H), 8.5(1H,s,=C-CH), 9.5(1H,s, br, CONH).
IV-c ₄	1700(cyclic amido), 1680(acyclic >C=O), 1620(>C=N), 1600(-O-).	1.35(3H,d,J=7.5Hz.,CH ₃), 2.35(3H,s, Ar-CH ₃), 3.80(3H,s, Ar-OCH ₃), 4.35(1H,q, J=7.5Hz.,CH), 6.9-8.15(12H,m, Ar-H), 8.7(1H,s,=C-CH), 9.3(1H,s, br, CONH).
IV-g ₆	1700(cyclic amido), 1680(acyclic >C=O), 1620(>C=N), 1600(-O-).	1.33H,d,J=7.5Hz.,CH ₃), 3.80(12 H,s, 3×OCH ₃), 4.3(1H,q, J=7.5Hz.,CH), 7.2-8.35(10H,m, Ar-H), 8.5(H,s,=C-CH), 9.5(1H,s, br, CONH).

Table 7. General characteristics and elemental analysis data of the compounds V-(a-c)₍₁₋₃₎

Comp.	R	R'	Yield %	M. P. °C	Mol. Formula	Elemental Analysis Found (Calcd) %		
						Carbon	Hydrogen	Nitrogen
V-a ₂	2-Me	4-Me	69	311	C ₂₇ H ₂₆ N ₄ O ₂ S	68.90 (68.91)	5.58 (5.57)	12.00 (11.91)
V-a ₃	2-Me	4-OMe	89	321	C ₂₇ H ₂₆ N ₄ O ₃ S	66.60 (66.65)	5.40 (5.39)	11.49 (11.51)
V-b ₁	3-Me	2-OH	84	301	C ₂₆ H ₂₄ N ₄ O ₃ S	66.05 (66.08)	5.10 (5.12)	11.79 (11.86)
V-b ₂	3-Me	4-Me	87	298	C ₂₇ H ₂₆ N ₄ O ₂ S	68.90 (68.91)	5.60 (5.57)	12.02 (11.91)
V-b ₃	3-Me	4-OMe	89	278	C ₂₇ H ₂₆ N ₄ O ₃ S	66.60 (66.65)	5.40 (5.39)	11.49 (11.51)
V-c ₁	4-Me	2-OH	77	288	C ₂₆ H ₂₄ N ₄ O ₃ S	66.09 (66.08)	5.14 (5.12)	11.89 (11.86)
V-c ₂	4-Me	4-Me	78	274	C ₂₇ H ₂₆ N ₄ O ₂ S	68.90 (68.91)	5.60 (5.57)	12.09 (11.91)
V-c ₃	4-Me	4-OMe	74	299	C ₂₇ H ₂₆ N ₄ O ₃ S	66.60 (66.65)	5.40 (5.39)	11.49 (11.51)
V-d ₁	3-Cl	2-OH	76	302	C ₂₅ H ₂₁ ClN ₄ O ₃ S	60.90 (60.91)	4.30 (4.29)	11.35 (11.36)
V-d ₂	3-Cl	4-Me	78	322	C ₂₆ H ₂₃ ClN ₄ O ₂ S	63.62 (63.60)	4.73 (4.72)	11.40 (11.41)
V-d ₃	3-Cl	4-OMe	89	310	C ₂₆ H ₂₃ ClN ₄ O ₃ S	61.60 (61.59)	4.58 (4.57)	11.06 (11.05)

V-e ₁	4-Cl	2-OH	85	289	C ₂₅ H ₂₁ ClN ₄ O ₃ S	60.94 (60.91)	4.31 (4.29)	11.31 (11.36)
V-e ₂	4-Cl	4-Me	84	296	C ₂₆ H ₂₃ ClN ₄ O ₂ S	63.62 (63.60)	4.73 (4.72)	11.40 (11.41)
V-e ₃	4-Cl	4-OMe	76	284	C ₂₆ H ₂₃ ClN ₄ O ₃ S	61.60 (61.59)	4.58 (4.57)	11.06 (11.05)
V-f ₁	3-OMe	2-OH	85	277	C ₂₆ H ₂₄ N ₄ O ₄ S	63.95 (63.90)	4.96 (4.95)	11.45 (11.47)
V-f ₂	3-OMe	4-Me	77	299	C ₂₇ H ₂₆ N ₄ O ₃ S	66.70 (66.65)	5.70 (5.39)	11.52 (11.51)
V-f ₃	3-OMe	4-OMe	88	324	C ₂₇ H ₂₆ N ₄ O ₄ S	64.52 (64.53)	5.22 (5.21)	11.17 (11.15)
V-g ₁	4-OMe	2-OH	89	311	C ₂₆ H ₂₄ N ₄ O ₄ S	63.95 (63.92)	4.97 (4.95)	11.48 (11.47)
V-g ₂	4-OMe	4-Me	88	309	C ₂₇ H ₂₆ N ₄ O ₃ S	66.70 (66.65)	5.70 (5.39)	11.52 (11.51)
V-g ₃	4-OMe	4-OMe	90	304	C ₂₇ H ₂₆ N ₄ O ₄ S	64.53 (64.53)	5.20 (5.21)	11.18 (11.15)

Table 8. Spectral characteristics of compounds from V-(a-g)₍₁₋₃₎

Comp.	IR vmax, cm ⁻¹	PMR δ , ppm.
V-a ₁	3320(phenolic OH), 1720(cyclic amido), 1680(acyclic >C=O), 1620(>C=N).	0.89(3H,s,=C- ₃), 1.45(3H,d,J=7.5Hz.,CH ₃), 2.25(3H,s, Ar-CH ₃), 4.3(1H,q, =7.5Hz.,CH), 7.3-8.3(12H,m, Ar-H), 9.5(1H,s, br, CONH), 12.5(1H,s, Broad, OH).
V-a ₃	1720(cyclic amido), 680(acyclic >C=O), 1620(>C=N), 1600(-O-).	0.95(3H,s,=C-H ₃), 1.45(3H,d,J=7.5Hz.,CH ₃), 2.25(3H,s, Ar-CH ₃), 3.80(3H,s,OCH ₃), 4.3(1H,q, J=7.5Hz.,CH), 7.1-8.4(12H, m, Ar-H), 9.5(1H,s, br, CONH).
V-c ₂	1720(cyclic amido), 680(acyclic >C=O), 1620(>C=N),	1.00(3H,s,=C-H ₃), 1.45(3H,d,J=7.5Hz.,CH ₃), 2.35(6H,s, Ar-CH ₃), 4.3(1H,q, J=7.5Hz.,CH), 6.9-8.15(12H, m, Ar-H), 8.6(1H,s, br, CONH).
V-f ₁	1720(cyclic amido), 680(acyclic >C=O), 1620(>C=N), 1600(-O-).	0.92(3H,s,=C-H ₃), 1.45(3H,d,J=7.5Hz.,CH ₃), 3.80(3 H,s, OCH ₃), 4.3(1H,q, J=7.5Hz.,CH), 7.3-8.3(12H,m, Ar-H), 9.5(1H,s, br, CONH), 12.5(1H,s, Broad, OH).

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