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Synthesis and QSAR Study of Some HDL Cholesterol Increasing Quinazolinone Derivatives

M.B.DESHMUKH* and SAVITA DHONGADE (DESAI).

Department of Chemistry,
Shivaji University, Kolhapur- 416004, India.

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Abstract: We describe here an easy and efficient method to obtain *s*-alkylated derivatives of thio-quinazolinone using different alkylating agents 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 hydrazones, 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 and HDL cholesterol increasing activities.

Keywords: Synthesis, QSAR study, Thio-quinazolinone

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 reactions[1]. The use of domestic microwave oven in this regard is now a well-established procedure in MORE[2] (microwave induced organic reaction enhancement) chemistry. It has been reported that the rate of variety of organic reactions such as Diels-Alder[3], ene[4], Claisen reaction[5], oxidation[6], reduction[7], diacetylation[8], deacetylation[9], deoximation[10], esterification[11], hydrolysis of

ester[12], Doebner condensation[13], Knoevenagel condensation[14]coulds 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 derivatives[15-17].

Quinazoline derivatives are of special importance because of their versatile biological & pharmacological activities[18-20], especially anti-inflammatory[21-23], anti-convulsant[24],hypnotic[25], anthemintic[26], hypo-tensive[27], antibacterial[28] agents etc. In the present work, *s*-alkylated derivatives of thio-quinazolinone were obtained using Ethyl chloroacetate 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)[29] 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

All m.ps. were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on Shimadzu IR-437 spectrophotometer and PMR spectra in $CDCl_3$ and DMSO-d_6 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-Mercapto-3-o-tolyl-3H-quinazolin-4-one (I a)

2-Mercapto-3-o-tolyl-3H-quinazolin-4-one (I a) was synthesized by a reported method[30] as follows.

The mixture of 2-methyl aniline (0.1 mole) was dissolved in benzene (12 mL) and carbon disulphide (11.7 mL, 0.15 mole) and triethylamine (15.45 g., 0.15 mole) stirred mechanically at 0^0C to get triethylammonium dithiocarbamate salt. The salt was then filtered, washed with dry ether, dried and crystallized from chloroform to get dithiocarbamate salts. Further the mixture of triethylammonium *N*- (2-methyl-phenyl) dithiocarbamate (0.05 mole) and anthranilic acid (7.2g., 0.05 mole)in ethanol (25 mL) was refluxed on a steam bath for 6 h, cooled and the separated solid was filtered and washed with water and further dissolved in 10% ethanolic sodium hydroxide solution, filtered and reprecipitated by the addition of dilute hydrochloric acid. The product obtained was filtered, washed with water and recrystallized from ethanol to give Ia. Yield: 89%, M.P.291^{o}C., Mol.Formula : $C_{15}H_{12}N_2OS$, Elemental analysis: C, 67.0(67.14 %) ; H, 4.5(4.51%) ; N, 10.5(10.44%), IR(KBr): νmax, 3320-3130 (-SH), 1690(cyclic amido >C=O),1625 cm^{-1}.(C=N), PMR(DMSO-d_6): δ, 2.9(3H,s,Ar-CH_3), 7.2-8.1(8H,m,Ar-H), 10.8(1H,s, exchangeable with D_2O,-SH) ppm.

Similarly, 2-Mercapto-3-m-tolyl-3H-quinazolin-4-one (I b), 2-Mercapto-3-p-tolyl-3H-quinazolin-4-one (I c), 3-(3-Chloro-phenyl)-2-mercapto-3H-quinazolin-4-one (I d),3-(4-Chloro-phenyl) -2- mercapto -3H – quinazolin -4-one (I e), 2 - Mercapto - 3- (3-methoxy-phenyl) -3H -quinazolin-4-one (I f) and 2-Mercapto-(4-methoxy-phenyl) -3H-quinazolin-4-one (I g) were synthesized.

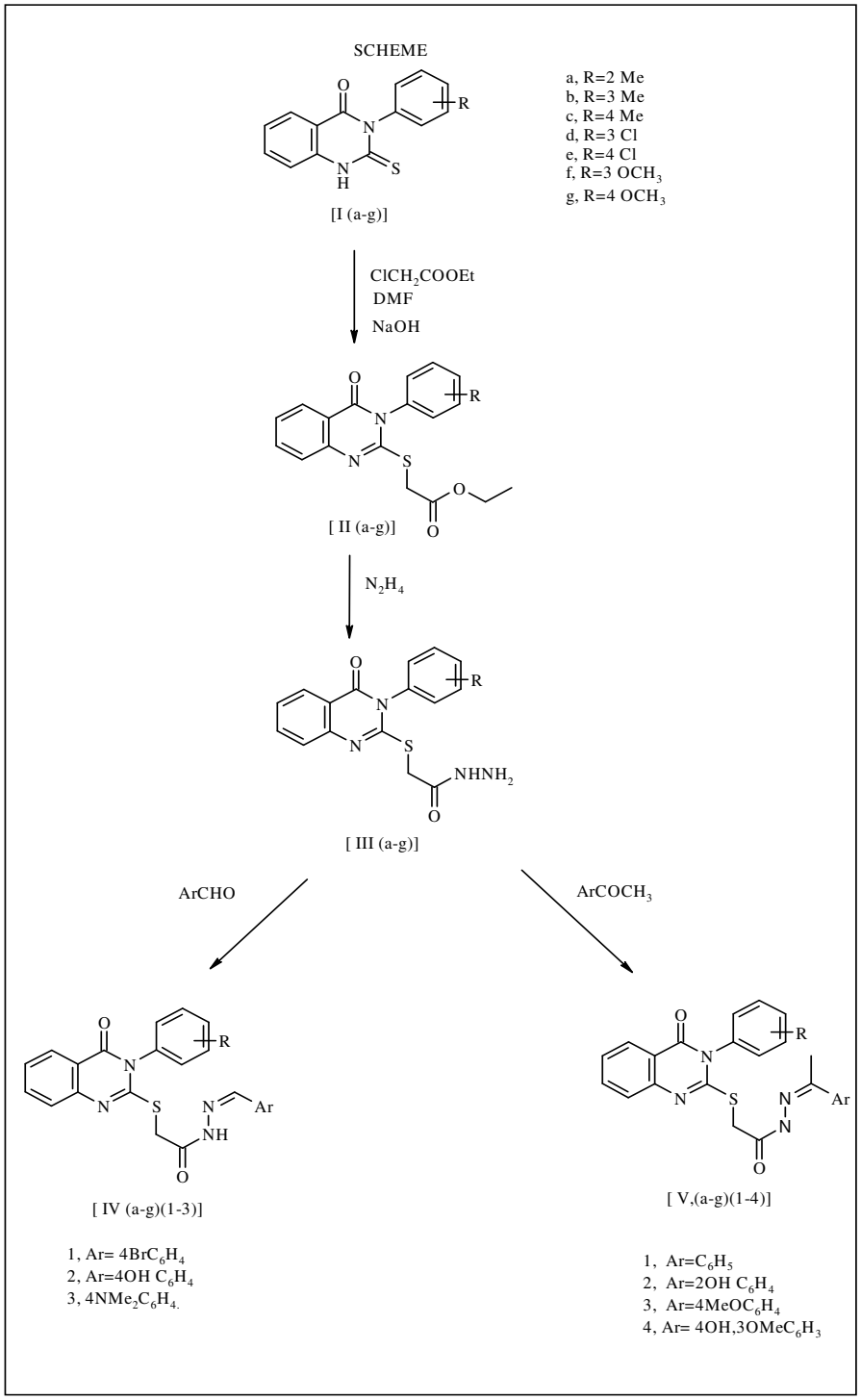
SCHEME
a, R=2 Me
b, R=3 Me
c, R=4 Me
d, R=3 Cl
e, R=4 Cl
f, R=3 OCH3
g, R=4 OCH3
[I (a-g)]
ClCH2COOEt
DMF
NaOH
[II (a-g)]
N2H4
[III (a-g)]
ArCHO
ArCOCH3
[IV (a-g)(1-3)]
1, Ar= 4BrC6H4
2, Ar=4OH C6H4
3, 4NMe2C6H4.
[V,(a-g)(1-4)]
1, Ar=C6H5
2, Ar=2OH C6H4
3, Ar=4MeOC6H4
4, Ar= 4OH,3OMeC6H3

Table 1. General characteristics and elemental analysis data of the compounds I (a-g)

Compound	Yield %	M.P °C	Mol. Formula	Carbon, % (found calcd)	Hydrogen, % (found calcd)	Nitrogen, % (found calcd)
I a	79	256	$C_{15}H_{12}N_2OS$	67.0 67.14	4.5 4.51	10.5 10.44
I b	89	268	$C_{15}H_{12}N_2OS$	67.10 67.14	4.54 4.51	10.45 10.44
I c	98	302	$C_{15}H_{12}N_2OS$	67.0 67.14	4.45 4.51	10.40 10.44
I d	85	270	$C_{14}H_9ClN_2OS$	58.2 58.23	3.1 3.14	9.8 9.70
I e	84	315	$C_{14}H_9ClN_2OS$	58.3 58.23	3.2 3.14	9.75 9.70
I f	86	280	$C_{15}H_{12}N_2O_2S$	63.3 63.36	4.2 4.25	9.8 9.85
I g	78	273	$C_{15}H_{12}N_2O_2S$	63.3 63.36	4.2 4.25	9.8 9.85

Table 2.Spectral Characteristics

Comp	IR νmax ,cm^{-1}	PMR δ, ppm.
Ib	3380-3200(-SH), 1680-1670 (cyclic amido >C=O), 1625 (C=N),	3.80(3H,s,CH_3), 6.9-7.9(8H,m,Ar-H),11.9(1H,s,Br. Exchangeable with D_2O,NH)
Ic	3150-3200(-NH),1680 (cyclic amido >C=O), 1620 (C=N),	2.3(3H,s,CH_3), 7.8-7.9(8H,m,Ar-H),11.3(1H,s,br. Exchangeablewith D_2O,NH)
Id	3325-3135(-NH), 1690 (cyclic amido >C=O), 1625 (C=N), 760(C-Cl)	7.2-8.1(8H,m,Ar-H), 12.8(1H,s,br, exchangeable with D_2O,NH)
Ie	3150-3200(-NH), 1680 (cyclic amido >C=O), 1620 (C=N), 760(C-Cl)	7.5-8.3(8H,m, Ar-H), 12.8(1H,s,br, exchangeable with D_2O,NH)
If	3250-3125(-NH), 1675-1680 (cyclic amido >C=O), 1620 (C=N),1060(-O-)	3.7(3H,s,OCH_3), 6.7-8.15(8H,m,Ar-H),12.9(1H,s,br, exchangeable with D_2O,NH)
Ig	3315-3125(-NH), 1680 (cyclic amido >C=O), 1625 (C=N),(-O-)	3.8(3H,s,OCH_3), 6.8-8.25(8H,m,Ar-H),13.0(1H,s,br, exchangeable with D_2O,NH)

[4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid ethyl ester [II a]

2.5 mmol of (Ia), (2.5) mmol of ethyl chloroacetate and 1 mmol of DMF and powdered NaOH (0.5 g), were 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. The mixture was added with 2N HCl (10 mL). The solid separated was filtered, conveniently dried and recrystallized of water to get IIa_1.Yield 79%, M.P.142^oC, Molecular formula $C_{19}H_{18}N_2O_3S$, elemental analysis C,64.5 (64.41); H, 5.0 (5.08); N, 7.8 (7.91). IR(KBr): νmax, 1750(C=O),1710(cyclic C=O), 1620 cm^{-1} (C=N), PMR(DMSO-d_6): δ, 1.3(3H,t J=7Hz. ,CH_3),2.9(3H,s,Ar-CH_3)3.64 (2H,s,-SCH_2), 4.3(2H,q J=7Hz.,CH_2), 7.5-8.2(8H,m,Ar-H) ppm.

Similarly,[4-Oxo-3-m-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid ethyl ester (II b), [4-Oxo-3-p-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid ethyl ester (II c), [3-(3-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]acetic acid ethyl ester (II d), [3-(4-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl] acetic acid ethyl ester (II e),),[3-(3-methoxy-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]acetic acid ethyl ester (II f) and [3-(4-methoxy-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]acetic acid ethyl ester (II g) were synthesized .Their structures were confirmed on the basis of elemental and spectral characteristics.

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

Compound	Yield %	M.P. ^oC	Mol. Formula	Carbon %(found calcd)	Hydrogen %(found calcd)	Nitrogen %(found calcd)
IIa	79	142	$C_{19}H_{18}N_2O_3S$	64.4 64.39	5.1 5.12	7.85 7.90
IIb	86	123	$C_{19}H_{18}N_2O_3S$	64.35 64.39	5.11 5.12	7.92 7.90
IIc	89	102	$C_{19}H_{18}N_2O_3S$	64.42 64.39	5.20 5.12	7.91 7.90
IId	84.5	86	$C_{18}H_{15}ClN_2O_3S$	57.5 57.68	4.00 4.03	7.4 7.47
IIe	89	98	$C_{18}H_{15}ClN_2O_3S$	57.59 57.68	4.10 4.03	7.45 7.47
IIf	79	126	$C_{19}H_{18}N_2O_4S$	61.6 61.61	4.89 4.90	7.50 7.56
IIg	85	122	$C_{19}H_{18}N_2O_4S$	61.56 61.61	4.85 4.90	7.53 7.56

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

IIa (0.1 mole) was mixed with 0.1 mole of hydrazine hydrate in 5mL of methanol and refluxed on a steam bath for three hours. The separated solid was filtered and recrystalized from ethanol to get IIIa. Yield 84%, M.P. 185^oC, Mol. Wt.= 340,Mol. Formula :$C_{17}H_{16}N_4O_2S$, Elemental Analysis:C,59.9(59.98)%); H,4.70(4.74%); 16.99(16.96%), IR (KBr): νmax, 3300-3250 ($NHNH_2$), 1680(>C=O), 1660 (>C=O),1620 cm^{-1} (C=N), PMR (DMSO-d_6): δ, 2.9(3H,s, Ar-CH_3), 3.74(2H,s,SCH2), 4.45 (1H,q, J=8.5Hz, -4.35 (2H,s,NH_2), 7.4-8.2(8H,m,Ar-H), 9.55 (1H, s, CONH) ppm.

Similarly, (4-Oxo-3-m-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid hydrazide (III b),(4-Oxo-3-p-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid hydrazide (III c), [3-(3-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid hydrazide (III d), [3-(4-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid hydrazide (III e), [3-(3-Methoxy -phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid hydrazide (III f) and [3-(4-Methoxy-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid hydrazide (III g) were synthesized.

Table 4. General characteristics and elemental analysis data of the compounds III (a-g)

Compound	Yield %	M.P. °C	Mol. Formula	Carbon %, (found Calcd)	Hydrogen %, (found Calcd)	Nitrogen %, (found Calcd)
IIIb	90	168	$C_{17}H_{16}N_4O_2S$	59.2 59.98	4.68 4.74	16.51 16.46
IIIc	86	148	$C_{17}H_{16}N_4O_2S$	60.0 59.98	4.75 4.74	16.45 16.46
IIId	87	186	$C_{16}H_{13}ClN_4O_2S$	53.2 53.26	3.6 3.63	15.5 15.53
IIIe	84	175	$C_{16}H_{13}ClN_4O_2S$	53.25 53.26	3.61 3.63	15.55 15.53
IIIf	88	156	$C_{17}H_{16}N_4O_3S$	57.2 57.29	4.5 4.53	15.8 15.72
IIIg	89	149	$C_{17}H_{16}N_4O_3S$	57.27 57.29	4.51 4.53	15.71 15.72

(4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (4- bromobenzyle -dene)hydrazide (IV a-1)

0.1 mole of III a and 0.1 mole of 4-bromobenzaldehyde , 5mL of DMF and few drops of acetic acid were smoothly mixed 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. The solid separated was filtered, conveniently dried and recrystallized of water to get IVa. Yield 88%, M.P. 322°C., Mol. Formula : $C_{24}H_{19}BrN_4O_2S$, Elemental analysis: Carbon, 56.8(56.81%); Hydrogen, 3.7(3.77%); Nitrogen, 11.0(11.04 %) ,IR (KBr): νmax, 1720(cyclic amido), 1680(acyclic >C=O), 1610 cm^{-1}.(C=N), PMR(DMSO-d_6): δ,2.9(3H,s,Ar-CH_3), 3.74(2H,s,SCH_2),7.3-8.3(12H,m,Ar-H), 9.6(1H,s,CONH) ppm.

Similarly,(4-Oxo-3-m-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (4-bromo-benzyledene)-hydrazide (IVb-1), (4-Oxo-3-p-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (4-bromo-benzyledene)-hydrazide (IVc-1), (4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (4-hydroxy -benzyledene)-hydrazide (IVa-2), (4-Oxo-3-m-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (4-hydroxy-benzyledene)-hydrazide (IVb-2),(4-Oxo-3-p-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (4-hydroxy -benzyledene)-hydrazide (IVc-2), (4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (4 - dimethylamino - benzyledene) - hydrazide (IVa-3), (4-Oxo-3-*m*-tolyl-3,4-

dihydro-quinazolin-2-ylsulfanyl)-acetic acid (4-dimethylamino-benzyledene)-hydrazide (IVb-3), (4-Oxo-3-p-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (4-dimethylamino-benzyledene)-hydrazide (IVc-3), [3-(3-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-bromo-benzyledene)-hydrazide (IV d-1), [3-(4-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-bromo-benzyledene)-hydrazide (IV e-1), [3-(3-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-hydroxy-benzyledene)hydrazide (IV d-2), [3-(4-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-hydroxy-benzyledene) hydrazide (IVe-2), [3-(3-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-dimethylamino- benzyledene)-hydrazide (IV d-3), [3-(4-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-dimethylamino -benzyledene)-hydrazide (IV e-3), [3-(3-Methoxy-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-bromo-benzyledene)-hydrazide (IV f-1), [3-(4-Methoxy -phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-bromo-benzyledene)-hydrazide (IV g-1), [3-(3-Methoxy-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-hydroxy-benzyledene)-hydrazide (IV f-2), [3-(4-Methoxy -phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-hydroxy-benzyledene)-hydrazide (IVg-2), [3-(3-Methoxy-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-dimethylamino-benzyledene)-hydrazide (IVf-3), [3-(4-Methoxy-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid (4-dimethylamino -benzyledene)-hydrazide (IVg-3) were synthesised and subjected to PASS for prediction of biological activities.

Table 5. General characteristics and elemental analysis data of the compounds IV (a-g)(1-3)

Compound	Yield %	M.P. ^{o}C	Mol. Formula	Carbon %, (found Calcd)	Hydrogen %, (found Calcd)	Nitrogen %, (found Calcd)
IV a-1	88	322	$C_{24}H_{19}BrN_4O_2S$	56.8 56.81	3.7 3.77	11.0 11.04
IV a-2	85	248	$C_{24}H_{20}N_4O_3S$	64.84 64.85	4.45 4.54	12.58 12.6
IV a-3	84	298	$C_{26}H_{25}N_5O_2S$	66.21 66.22	5.31 5.34	14.91 14.85
IV b-1	95	267	$C_{24}H_{19}BrN_4O_2S$	56.82 56.81	3.72 3.77	11.08 11.04
IV b-2	86	251	$C_{24}H_{20}N_4O_3S$	64.84 64.85	4.60 4.54	12.61 12.6
IV b-3	74	236	$C_{26}H_{25}N_5O_2S$	66.24 66.22	5.34 5.34	14.92 14.85
IV c-1	85	214	$C_{24}H_{19}BrN_4O_2S$	56.83 56.81	3.72 3.77	11.10 11.04
IV c-2	96	268	$C_{24}H_{20}N_4O_3S$	64.83 64.85	4.51 4.54	12.58 12.6
IV c-3	89	298	$C_{26}H_{25}N_5O_2S$	66.23 66.22	5.36 5.34	14.91 14.85

Compound	Yield %	M.P. °C	Mol. Formula	Carbon %, (found Calcd)	Hydrogen %, (found Calcd)	Nitrogen %, (found Calcd)
IV d-1	87	302	$C_{23}H_{16}BrClN_4O_2S$	52.3 52.36	3.0 3.06	10.56 10.61
IV d-2	85	300	$C_{23}H_{17}ClN_4O_3S$	60.0 59.42	3.7 3.69	12.0 12.03
IV d-3	86	298	$C_{25}H_{22}ClN_5O_2S$	61.0 61.03	4.5 4.51	14.3 14.23
IV e-1	89	248	$C_{23}H_{16}BrClN_4O_2S$	52.3 52.36	3.0 3.06	10.56 10.61
IV e-2	84	269	$C_{23}H_{17}ClN_4O_3S$	60.0 59.42	3.7 3.69	12.0 12.03
IV e-3	87	289	$C_{25}H_{22}ClN_5O_2S$	61.0 61.03	4.5 4.51	14.3 14.23
IV f-1	86	278	$C_{24}H_{19}BrN_4O_3S$	55.0 55.07	3.7 3.66	10.65 10.70
IV f-2	82	289	$C_{24}H_{20}N_4O_4S$	62.7 62.60	4.4 4.38	12.2 12.17
IV f-3	81	269	$C_{26}H_{25}N_5O_3S$	64.0 64.05	5.2 5.17	14.4 14.36
IV g-1	74	255	$C_{24}H_{19}BrN_4O_3S$	55.08 55.07	3.70 3.66	10.69 10.70
IV g-2	79	294	$C_{24}H_{20}N_4O_4S$	62.62 62.60	4.34 4.38	12.12 12.17
IV g-3	95	266	$C_{26}H_{25}N_5O_3S$	64.10 64.05	5.21 5.17	14.34 14.36

(4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid [1-(2-hydroxy-phenyl)-ethyledene]-hydrazide (V a-2)

0.1 mole of III a and 0.1 mole of 1-(2-hydroxy phenyl) acetone , 5mL of DMF and few drops of acetic acid were smoothly mixed and 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 of ethanol to get V a-2. Yield 88%, M.P. 358°C., Mol.Formula : $C_{25}H_{22}N_4O_3S$, Elemental analysis: Carbon, 67.8(67.85%); Hydrogen,5.0(5.01%); Nitrogen,12.7(12.66%), IR (KBr): νmax, 1720(cyclic amido), 1680(acyclic >C=O), 1610 cm^{-1}.(C=N), PMR(DMSO-d_6):δ,2.1(3H,s,=CCH_3),2.9(3H,s,Ar-CH_3), 3.74(2H, s,SCH_2), 7.3-8.3(12H,m,Ar-H), 9.6(1H,s,CONH), 12.5(1H,s,br, OH) ppm.

Table 6. Spectral Characteristics

Comp.	IR νmax ,cm^{-1}	PMR δ, ppm.
IV b-3	1720(cyclic amido), 1680(acyclic >C=O), 1620(>C=N).	2.5(3H,s, Ar-CH_3),3.15 (6H,s, $N(CH_3)_2$) 3.73(2H,s, SCH_2), 7.2-8.2(12H,m,Ar-H), 8.5(1H,s,=C-CH),9.5(1H,s, CONH),
IV c-3	1720(cyclic amido), 1680(acyclic >C=O), 1620(>C=N).	2.9(3H,s, Ar-CH_3),3.15 (6H,s, $N(CH_3)_2$) 3.76(2H,s, SCH_2),7.5-8.5(12H,m,Ar-H), 8.8(1H,s,=C-CH),9.8(1H,s, CONH),
IV d-2	3320(phenolic OH) 1720(cyclic amido), 1680(acyclic >C=O), 1620(>C=N)	3.72(2H,s, SCH_2),7.3-8.3(12H,m,Ar-H), 8.6(1H,s,=C-CH),9.5(1H,s, CONH), 12.5(1H,s, Broad, OH).
IV g-1	1720(cyclic amido), 1680(acyclic >C=O), 1620(>C=N),1600(-O-)	3.72(2H,s, SCH_2),3.77(3H,s, OCH_3), 7.3-8.3(12H,m, Ar-H),8.6(1H,s, =C-CH), 9.5(1H,s, CONH),

Similarly, (4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (1-phenyl)-ethyledene]-hydrazide(V a-1), (4-Oxo-3-m-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (1-phenyl)-ethyledene]-hydrazide(V b-1), (4-Oxo-3-p-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (1-phenyl)-ethyledene]-hydrazide(Vc-1), (4-Oxo-3-m-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid [1-(2-hydroxy-phenyl)-ethyledene]-hydrazide(V b-2), (4-Oxo-3-p-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid [1-(2-hydroxy-phenyl)-ethyledene]-hydrazide(V c-2), (4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid [1-(4-methoxy-phenyl)-ethyledene]-hydrazide(Va-3), (4-Oxo-3-m-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid [1-(4-methoxy-phenyl)-ethyledene]-hydrazide(Vb-3), (4-Oxo-3-p-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid [1-(4-methoxy-phenyl)-ethyledene]-hydrazide(Vc-3), (4-Oxo-3-o-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid [1-(4-hydroxy-3-methoxy-phenyl)-ethyledene]-hydrazide(Va-4), (4-Oxo-3-m-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid [1-(4-hydroxy-3-methoxy-phenyl)-ethyledene]-hydrazide(Vb-4), (4-Oxo-3-p-tolyl-3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid [1-(4-hydroxy-3-methoxy-phenyl)-ethyledene]-hydrazide(V c-4),[3-(3-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid(1-phenyl-ethyledene)-hydrazide(Vd-1), [3-(4-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid(1-phenyl-ethyledene)-hydrazide(Ve-1), [3-(3-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(2-hydroxy-phenyl)-ethyledene)-hydrazide(Vd-2), [3-(4-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(2-hydroxy-phenyl)-ethyledene)-hydrazide(Ve-2), [3-(3-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(4-methoxy –phenyl)-ethyledene)-hydrazide(Vd-3), [3-(4-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(4-methoxy –phenyl)-ethyledene)-hydrazide(Ve-3), [3-(3-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(4-hydroxy-3-methoxy-phenyl-ethyledene)-hydrazide(Vd-4), [3-(4-Chloro-phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(4-hydroxy-3-methoxy-phenyl-ethyledene)-hydrazide(Ve-4), [3-(3-Methoxy -phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid(1-phenyl-ethyledene)-hydrazide(V f-1), [3-(4-Methoxy -phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid(1-phenyl-ethyledene)-hydrazide(V g-1),

[3-(3- Methoxy -phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(2-hydroxy-phenyl)-ethyledene)-hydrazide(Vf-2), [3-(4- Methoxy -phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(2-hydroxy-phenyl)-ethyledene)-hydrazide(Vg-2), [3-(3- Methoxy -phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(4-methoxy –phenyl)-ethyledene)-hydrazide(Vf-3), [3-(4- Methoxy -phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(4-methoxy –phenyl)-ethyledene)-hydrazide(Vg-3), [3-(3- Methoxy -phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(4-hydroxy-3-methoxy-phenyl-ethyledene)-hydrazide(Vf-4) and [3-(4- Methoxy -phenyl)-4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl]-acetic acid[1-(4-hydroxy-3-methoxy-phenyl-ethyledene)-hydrazide(Vg-4) were synthesised and studied for their elemental analysis and characteristic properties and subjected to PASS for prediction of biological activities.

Table 7. General characteristics and elemental analysis data of the compounds V (a-c)(1-4)

Compound	Yield %	M.P. °C	Mol. Formula	Carbon %, (found Calcd)	Hydrogen %, (found Calcd)	Nitrogen %, (found Calcd)
V a-1	86	289	$C_{25}H_{22}N_4O_2S$	67.8 67.85	5.0 5.01	12.7 12.66
V a-2	88	358	$C_{25}H_{22}N_4O_3S$	65.5 65.49	4.8 4.84	12.3 12.22
V a-3	76	269	$C_{26}H_{24}N_4O_3S$	66.0 66.08	5.1 5.12	11.9 11.86
V a-4	79	298	$C_{26}H_{24}N_4O_4S$	63.9 63.92	4.99 4.95	11.5 11.47
V b-1	85	325	$C_{25}H_{22}N_4O_2S$	67.8 67.85	5.0 5.01	12.7 12.66
V b-2	74	321	$C_{25}H_{22}N_4O_3S$	65.5 65.49	4.8 4.84	12.3 12.22
V b-3	89	314	$C_{26}H_{24}N_4O_3S$	66.0 66.08	5.1 5.12	11.9 11.86
V b-4	96	322	$C_{26}H_{24}N_4O_4S$	63.8 63.92	4.92 4.95	11.48 11.47
V c-1	85	301	$C_{25}H_{22}N_4O_2S$	67.8 67.85	5.0 5.01	12.7 12.66
V c-2	84	289	$C_{25}H_{22}N_4O_3S$	65.5 65.49	4.8 4.84	12.3 12.22
V c-3	88	279	$C_{26}H_{24}N_4O_3S$	66.0 66.08	5.1 5.12	11.9 11.86
V c-4	75	299	$C_{26}H_{24}N_4O_4S$	63.88 63.92	4.96 4.95	11.45 11.47

Table 8. General characteristics and elemental analysis data of the compounds V (d,e)(1-4)

Compound	Yield %	M.P. °C	Mol. Formula	Carbon %, (found Calcd)	Hydrogen %, (found Calcd)	Nitrogen %, (found Calcd)
V d-1	71	300	$C_{24}H_{19}ClN_4O_2S$	62.2 62.27	4.1 4.14	12.2 12.10
V d-2	75	302	$C_{24}H_{19}ClN_4O_3S$	60.10 60.19	4.10 4.00	11.80 11.70
V d-3	85	305	$C_{25}H_{21}ClN_4O_3S$	61.00 60.91	4.30 4.29	11.40 11.36
V d-4	86	325	$C_{25}H_{21}ClN_4O_4S$	58.9 59.0	4.20 4.16	11.00 11.01
V e-1	86	321	$C_{24}H_{19}ClN_4O_2S$	62.2 62.27	4.10 4.14	12.2 12.10
V e-2	82	341	$C_{24}H_{19}ClN_4O_3S$	60.15 60.19	4.10 4.00	11.81 11.70
V e-3	83	289	$C_{25}H_{21}ClN_4O_3S$	61.10 60.91	4.21 4.29	11.35 11.36
V e-4	91	257	$C_{25}H_{21}ClN_4O_4S$	58.89 59.0	4.21 4.16	11.10 11.01

Table 9. General characteristics and elemental analysis data of the compounds V (f,g)(1-4)

Compound	Yield %	M.P. °C	Mol. Formula	Carbon %(found calcd)	Hydrogen %(found calcd)	Nitrogen %(found calcd)
V f-1	72	288	$C_{25}H_{22}N_4O_3S$	65.50 65.49	4.88 4.84	12.25 12.22
V f-2	85	259	$C_{25}H_{22}N_4O_4S$	63.23 63.28	4.70 4.67	11.78 11.81
V f-3	90	222	$C_{26}H_{24}N_4O_3S$	64.02 63.92	5.00 4.95	11.51 11.47
V f-4	88	269	$C_{26}H_{24}N_4O_4S$	61.88 61.89	4.72 4.79	11.00 11.10
V g-1	74	299	$C_{25}H_{22}N_4O_3S$	65.51 65.49	4.89 4.84	12.23 12.22
V g-2	71	278	$C_{25}H_{22}N_4O_4S$	63.33 63.28	4.67 4.67	11.82 11.81
V g-3	73	274	$C_{26}H_{24}N_4O_3S$	64.11 63.92	5.10 4.95	11.45 11.47
V g-4	82	275	$C_{26}H_{24}N_4O_4S$	61.91 61.89	4.78 4.79	11.20 11.10

Table 10. Spectral Characteristics

Comp.	IR νmax ,cm^{-1}	PMR δ, ppm.
V a-1	1720(cyclic amido), 1680(acyclic >C=O), 1620(>C=N).	2.1(3H,s, $=CCH_3$),2.5(3H,s, Ar-CH_3), 3.73(2H,s, SCH_2),7.2-8.2(13H,m,Ar-H), 9.5(1H,s, CONH),
V a-3	1720(cyclic amido), 1680(acyclic >C=O), 1620(>C=N),1600(-O-).	2.2(3H,s, $=CCH_3$)2.6(3H,s, Ar-CH_3), 3.76(2H,s, SCH_2),7.5-8.5(12H,m,Ar-H), 9.8(1H,s, CONH),
V c-2	3310(phenolic OH) 1720(cyclic amido), 1680(acyclic >C=O), 1620(>C=N)	2.1(3H,s, $=CCH_3$),2.8(3H,s, Ar-CH_3), 3.72(2H,s, SCH_2),7.3-8.3(12H,m,Ar-H), 9.5(1H,s, CONH),12.5(1H,s, Broad, OH).
V e-1	1720(cyclic amido), 1680(acyclic >C=O), 1620(>C=N).	2.3(3H,s, $=CCH_3$),3.72(2H,s, SCH_2), 7.3-8.3(12H,m, Ar-H),9.5(1H,s, CONH),

Table 11.QSAR Analysis of Activities with Pa>70%3 Possible activities at Pa>70%

Activity ☞ Compounds☟	[1]Pa	[1]Pi	[2]Pa	[2]Pi	[3]Pa	[3]Pi	[4]
IV a-1	0,838	0,004	0,780	0,004	0,757	0,005	48
IV a-2	0,822	0,005	0,754	0,004	0,740	0,005	50
IV a-3	0,818	0,005	0,746	0,005	0,746	0,005	49
IV b-1	0,804	0,006	0,785	0,004	0,768	0,005	49
IV b-2	0,781	0,007	0,758	0,004	0,751	0,005	51
IV b-3	0,774	0,007	0,751	0,005	0,756	0,005	50
IV c-1	0,809	0,006	0,792	0,004	0,775	0,005	48
IV c-2	0,786	0,006	0,764	0,004	0,756	0,005	50
IV c-3	0,780	0,007	0,756	0,004	0,762	0,005	49
IV d-1	0,821	0,005	0,775	0,004	0,759	0,005	50
IV d-2	0,802	0,006	0,751	0,005	0,744	0,005	52
IV d-3	0,797	0,006	0,743	0,005	0,749	0,005	51
IV e-1	0,818	0,005	0,782	0,004	0,765	0,005	49
IV e-2	0,798	0,006	0,757	0,004	0,749	0,005	51
IV e-3	0,793	0,006	0,749	0,005	0,754	0,005	50
IV f-1	0,787	0,006	0,759	0,004	0,744	0,005	53
IV f-2	0,766	0,007	0,748	0,005	0,739	0,005	53
IV f-3	0,752	0,007	0,731	0,005	0,734	0,005	54
IV g-1	0,792	0,006	0,764	0,004	0,748	0,005	52
IV g-2	0,772	0,007	0,752	0,005	0,743	0,005	52
IV g-3	0,758	0,007	0,735	0,005	0,738	0,005	53

[1] HDL-cholesterol increasing [3] Antimycobacterial
[2] Antituberculosic [4] Substructure descriptors

Table 12. QSAR Analysis of compounds V(a-g)(1-4)Activities with Pa>70%Only 1 Possible activitiy at Pa>70%HDL-cholesterol increasing Activity

Compound	Pa	Pi	Substructure Descriptors
V a-1	0.838	0.004	43
V a-2	0.821	0.005	50
V a-3	0.818	0.005	51
V a-4	0.808	0.006	57
V b-1	0.800	0.006	44
V b-2	0.781	0.007	51
V b-3	0.776	0.007	52
V b-4	0.765	0.007	58
V c-1	0.806	0.006	43
V c-2	0.786	0.006	50
V c-3	0.781	0.007	51
V c-4	0.770	0.007	57
V d-1	0.818	0.005	46
V d-2	0.800	0.006	53
V d-3	0.797	0.006	54
V d-4	0.787	0.006	60
V e-1	0.815	0.005	45
V e-2	0.797	0.006	53
V e-3	0.793	0.006	53
V e-4	0.782	0.007	59
V f-1	0.780	0.007	49
V f-2	0.766	0.007	54
V f-3	0.780	0.007	49
V f-4	0.766	0.007	56
V g-1	0.785	0.006	48
V g-2	0.772	0.007	53
V g-3	0.785	0.006	48
V g-4	0.771	0.007	55

Conclusions

The compounds of the type (4-Oxo-3-aryl -3,4-dihydro-quinazolin-2-ylsulfanyl)-acetic acid (substituted-benzyledene)-hydrazide IV (a-g)(1-3) 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 4-bromobenzaldehyde are expected to exhibit spectacular HDL Cholesterol Increasing activity. Other derivatives are also expected to exhibit good HDL Cholesterol Increasing activity. Hence these compounds are recommended for the screening of HDL Cholesterol Increasing activity. When the relationship between the structure and anti-tuberculosic

activity was studied, it was found that the 3-methylphenyl, 4-methyl-phenyl,3-chloro-phenyl and 4-chlorophenyl quinazolinone derivatives condensed with 4-bromobenzaldehyde are expected to exhibit spectacular anti-tuberculosic activity. Whereas, other derivatives are also expected to exhibit good anti-tuberculosic activity.Hence these compounds are recommended for the screening of anti-tuberculosic activity .

QSAR study of the compounds was similarly done for the anti-mycobacerial activities. It was found that 3-methylphenyl, 4-methyl-phenyl and 4-chloro-phenyl quinazolinone derivatives condensed with 4-bromobenzaldehyde are expected to exhibit spectacular anti-mycobacterial activity. Whereas, other derivatives are also expected to exhibit good anti-mycobacterial activity. Hence these compounds were recommended for the screening of anti-mycobacterial activity too.

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 R_1=2-Me are expected to exhibit spectacular HDL cholesterol increasing activity. Whereas the derivatives of quinazolinones condensed with unsubstituted benzophenone were found to be more probably active as compared with those with substituted ones. In fact the quinazolinones condensed with different aromatic ketones are expected to be exhibit more HDL cholesterol activity as compared to those with aldehydes.

Hence these compounds were recommended for the screening of HDL Cholesterol Increasing activity, anti-tuberculosic activity anti-mycobacterial activity too.

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