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Der Pharma Chemica, 2010, 2(3): 267-276
(<http://derpharmachemica.com/archive.html>)



Synthesis , reactions and antimicrobial activity on some novel phthalazinone derivatives

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Abstract

A simple and efficient synthesis of [4-(3, 4-dimethylphenyl)-5, 6, 7, 8-tetrabromo-1-oxo-1H-phthalazin-2-yl]-acetic acid hydrazide (IV) has been carried out. The obtained hydrazide (IV) has been used in synthesis of some interesting heterocycles such as pyrazolone, thiazolidinone, pyrimidine, benzoxazine lactam, rhodanine, quinazoline, benzoxazinone (VIII–XVII). Some of the prepared compounds tested for in vitro antibacterial activities. Among those tested, many compounds showed good antibacterial activities.

Keywords: Phthalazinone, Pyrazolone, Thiazolidinone, Azitidinone, Quinazoline, Pyrimidine derivatives and antimicrobial activity

INTRODUCTION

The synthesis of new heterocycles containing phthalazine moiety are examples of nitrogen heterocycles that possess exciting biological properties [1-3].

Phthalazine have been reported to possess anticonvulsant[4-6] , antifungal activity[7] and vasorelaxant activities⁸ . Additionally, phthalazines have recently been reported to potentially inhibit serotonin reuptake and are considered as anti-depression agents [9,10] .

RESULT AND DISCUSSION

In the present work, the phthalazine derivative (II) has been obtained via the condensation of the aroyl benzoic acid (I) with hydrazine hydrate in boiling ethanol^{11,12}. The structure of (II) was inferred from elemental analysis and the IR spectrum, which showed stretching bands at 3309 , 1706 and 1620 cm^{-1} corresponding to NH ,C=O and C=N groups respectively. The ^1H NMR spectrum revealed the appearance of singlet signal at δ 7.2 ppm attributed to the amidic proton (NH-CO), in addition to signals at δ 7.45-7.67 ppm attributed to 3 aromatic protons and singlet at 2.34(s,6H,2Ar-CH₃).EIMS showed the molecular ion peak at m/z 566.

Substituted Phthalazine was prepared by reacting of (II) with chloroacetyl chloride to give chloroacetyl derivative (III). The IR spectrum of compound (III) showed stretching bands at 1751, 1685 cm^{-1} corresponding to the C=O of acid chloride and the C=O of cyclic amide. The ^1H NMR spectrum of compound (III) revealed singlet at δ 2.34 attributed to the two methyl protons and the methylenic protons appeared at δ 4.75ppm (-N- CH_2 -CO) also the aromatic protons appeared at δ 7.45-7.67. such ^1H NMR data agreed well with the proposed structure.

The structure of the acid chloride derivative (III) was further supported by its reaction with hydrazine hydrate in boiling ethanol, the corresponding hydrazide derivative (IV) was obtained. The IR spectrum of (IV) which revealed the disappearance of C=O of acid chloride at 1751 cm^{-1} and the appearance of one broad band at 1705 cm^{-1} due to the C=O of amide and bands at 3263, 3312 cm^{-1} assigned to the NHNH_2 group. In addition, the EIMS spectrum of (IV) revealed m/z 553 which is consistent with M^+ -Br which decomposes to give the different fragments.

The hydrazide (IV) reacted with phenyl isocyanate¹³ in boiling benzene to give N-phenyl amino carbonyl [4-(3, 4-Dimethyl-phenyl)-5, 6, 7, 8-tetrabromo-1-oxo-2H-phthalazine-2-yl]-acetic acid hydrazide V. The IR spectrum, showed stretching bands at 3299 cm^{-1} corresponding to NH group. ^1H NMR spectrum exhibit multiplet signal at 7.45-7.67 due to 8 aromatic protons, singlet signal at 6.0 corresponding to NHNHCO protons and another singlet due to CONHC_6H_5 proton.

When the hydrazide (IV) and the acetyl acetone were fused together at 160 °C gave the acetyl acetone monohydrazone (VI). The structure of (VI) was confirmed from IR spectrum, showed stretching bands at 3127,1722,1704 and 1669 cm^{-1} due to NH, C=O of ketone, CO of amide and C=O of cyclic amide. The ^1H NMR spectrum exhibit singlet at 2.34 due to 3H of COCH_3 , 2.1ppm due to $\text{N}=\text{C}-\text{CH}_3$ and 2.5 ppm due to 2H of CH_2COCH_3 .

In a similar manner, fusion of a mixture of acetic acid hydrazide IV and acetic anhydride at 160 °C afforded acetoxy-N-acetyl-N'-[2-(4-(3,4-dimethyl-phenyl)-5,6,7,8-tetrabromo-1-oxo-2H-phthalazine-2-yl)-acetyl]-hydrazide (VII) in 60% yield. The formation of (VII) was confirmed by microanalytical and the IR spectrum which revealed the appearance of two bands at 1675, 1741 cm^{-1} due to the C=O of amide and acetoxy C=O groups respectively.

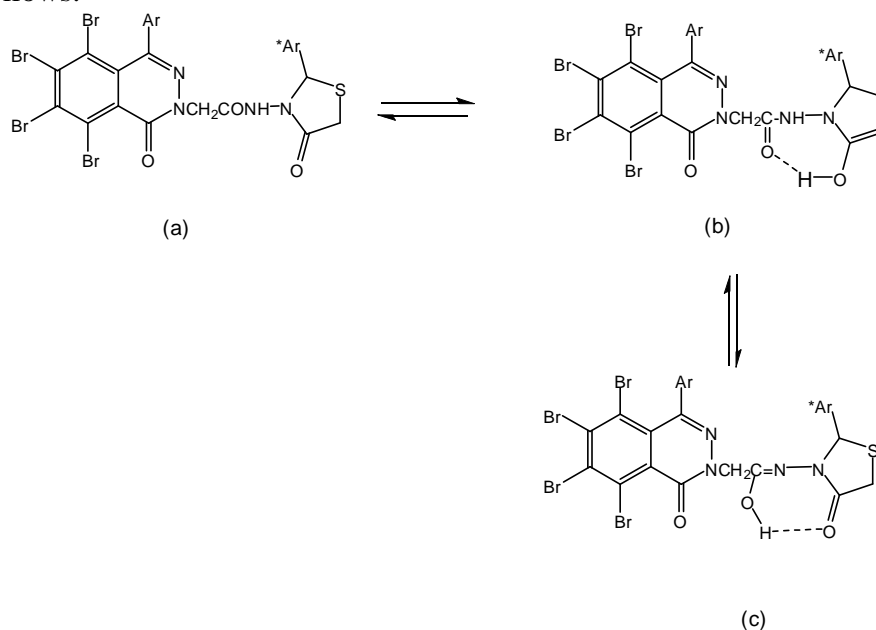
Cyclocondensation of the acid hydrazides (IV) with ethyl acetoacetate in absolute ethanol [14] afford 5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-2-[2-(5-methyl-3-oxo-2,3-dihydro-pyrazol-1-yl)-2-oxo-ethyl]-2H-phthalazin-1-one(VIII). The IR spectrum of (VIII) showed stretching bands at 3327, 1722 and 1665 cm^{-1} corresponding to OH and C=O groups respectively. The ^1H NMR spectrum of the compound (VIII) revealed the appearance of different singlet signals at δ 2.30, 2.34, 4.31 and 11.40 ppm corresponding to CH_3 , pyrazole, two Ar- CH_3 , NCH_2CO - and hydroxyl proton respectively. The EIMS spectrum revealed an $[\text{M}-2]^+$ at m/z 702.

It is interesting to investigate the behavior of the hydrazide (IV) towards aromatic aldehydes [15,16] to obtain corresponding arylidene (IX) which contain C=N to investigate its behavior towards aliphatic and aromatic mercaptans under Michael reaction conditions. Thus, treatment of compound (IV) with series of aldehydes such as anisaldehyde, furfural, p-chlorobenzaldehyde and piperonal, afforded [4-(3, 4-dimethyl-phenyl)-5,6,7,8-tetrabromo-1-oxo-2H-phthalazine-2-yl]-acetic acid [(1-aryl) methylidene] hydrazide derivatives (IXa-d).

The IR spectrum of **(IXa)** (Ar =C₆H₄-OCH₃) showed stretching bands at 3303 and 1704 cm⁻¹ corresponding to NH and C=O groups, respectively. The H¹NMR spectrum of **(IXc)** (Ar =C₆H₄-Cl) revealed the appearance of singlet signal at 6.46 ppm due to the olefinic proton of the methine group N=CH-Ar. The EIMS spectrum of **(IXc)** showed the two isotopic molecular ion peak at m/z 760,762 together with the fragmentation pattern complying with the structure assigned for the product.

The behavior of activated double bond in the hydrazone **(IXa)** towards sulphur nucleophiles has been studied¹⁷, in the present investigation when hydrazone **(IXa)** was allowed to react with thiophenol in the presence of a few drops of piperidine, the product **(X)** was formed. The IR spectrum of **(X)** exhibited stretching bands at 3170, 1722 and 1673 cm⁻¹ attributed to NH group and two C=O groups, respectively.

On the other hand, when the hydrazone **(IXa)** was allowed to react with thioglycolic acid, addition to C=N takes place first, followed by cyclization and the thiazole nucleus attached to the side chain of the phthalazine derivative **(XI)** was afforded. The IR spectrum of **XI** showed the presence of ν C=O of cyclic amide at 1680, 1647, ν NH at 3184 and ν OH at 3363 cm⁻¹. Such IR data illustrate that phthalazine **(XI)** is present into three tautomeric forms a, b and c as follows:



The tautomers (a) and (b) are stabilized via hydrogen bonding, while the tautomer (c) is more stable than (a) and (b) due to keto form which is more stable than enol form.[18,19]

Furthermore the author and others investigated the behavior of compound **(IX)** towards cycloaddition reactions¹⁷, thus chloroacetyl chloride cycloadded to the Schiff base **(IX)** in dry dioxane in the presence of tri ethyl amine as a catalyst to afford N-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-2-(5, 6, 7, 8-tetrabromo-4-(3, 4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl) acetamide **(XII)**. The IR spectrum displayed strong absorption bands at 3183 cm⁻¹ (NH), bands at 1701 and 1687 cm⁻¹ equivalent to(C=O) groups of cyclic amide and lactam ring respectively.

The compound **(IV)** could be converted into dithiocarbamate **(XIII)** when it stirred with a mixture of carbon disulfide and ammonium hydroxide at room temperature. the IR spectrum

showed strong absorption bands at 3423 cm^{-1} and 1267 cm^{-1} due to NH, C=S groups respectively. EIMS spectrum show (M^+) at m/z 729.

Conducting our interest in developing program for studying the behavior of dithiocarbamate compound (**XIII**) towards alkylating agents such as methyl iodide in order to prepare monomethyl (**XIV**) and dimethyl derivatives (**XV**).

Attempts were effort to cyclize the monomethyl compound (**XIV**) by refluxing with anthranilic acid afforded N-(4-oxo-2-thioxo-1,2-dihydro quinazolin-3(4H)-yl)-2-(5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl)acetamide (**XVI**). When the foregoing reaction was applied using potassium salt of anthranilic acid and dimethyl derivative (**XV**), N'-(4-oxo-1H-benzo[d][1,3]oxazin-2(4H)-ylidene)-2-(5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl) aceto hydrazide (**XVII**) was obtained.

The reaction of compound (**XIII**) with sodium chloroacetate in aqueous medium followed by acidification with concentrated hydrochloric acid afforded N-(4-oxo-2-thioxothiazolidin-3-yl)-2-(5, 6, 7, 8-tetrabromo-4-(3, 4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl) acetamide (**XVIII**). The IR spectrum showed strong absorption bands at 3323 cm^{-1} due to NH of hydrazine group, at 2857 & 2925 cm^{-1} due to CH aliphatic, at 1714 cm^{-1} attributable to C=O and at 1255 cm^{-1} characteristic for C=S group.

Antimicrobial activity

The antimicrobial activity of some of the synthesized compounds was determined *in vitro* against a variety of bacteria.

The tests were carried out using disc diffusion method[20].

The compounds were dissolved in DMF, and activity mentioned on 1000ppm. Agar plates were surface inoculated uniformly from fresh broth culture of the gram +ve and gram -ve bacteria.

The discs were incubated at 5°C for 1 h. to permit good diffusion then incubated at 28°C for 24 h, and the zones of inhibition were measured.

Table (1): Antimicrobial activity of some synthesized compounds IV, IXa, XI and XII.

Compound	Antibacterial activity			
	Gram +ve bacteria		Gram -ve bacteria	
	<i>Basillus Subtilis</i>	<i>Streptococci</i>	<i>Klebsiella Pneumoniea</i>	<i>Escherechia Coli</i>
IV	-	-	-	-
IXa	-	-	-	+
XI	+++	+++	++	+++
XII	+	+	++	++
Control	-	-	-	-

The data obtained in table (1) indicate that the starting compound (**IV**) is biologically inactive against gram +ve and gram -ve bacteria. The activity of thiazolidinone (**XI**) is higher than the activity of the rest of the prepared compounds while Schiff base (**IXa**) showed no activity against gram +ve bacteria and exhibit only weak activity with *Escherechia Coli*. The β -

lactam derivative (**XII**) has weak activity against Gram +ve bacteria while show moderate activity against Gram -ve bacteria.

Table (2): Antimicrobial activity of some synthesized compounds XIII, XVI, XVII and XVIII.

Compound	Antibacterial activity			
	Gram +ve bacteria		Gram -ve bacteria	
	Basillus Subtilis	Streptococci	Klebsiella Pneumoniae	Escherechia Coli
XIII	+++	-	+	-
XVI	+++	-	-	-
XVII	-	-	-	-
XVIII	++	-	+	-
Control	-	-	-	-

It is quite clear from table (2) that, the activity of the prepared compounds (**XIII, XVI, XVII and XVIII**) against gram +ve and gram –ve bacteria, can be arranged as follow:

- Using Streptococci and Escherechia Coli all the compounds showed no activity.
- Using Basillus Subtilis, the compounds (**XIII**) and (**XVI**) exhibit strong activity, the decrease in potency is noticed as we pass from rodanone ring (**XVIII** to **XVII**).
- Using *Klebsiella Pneumoniae*, all the compounds are inactive except (**XIII** and **XVI**) that showed weak activity.

CONCLUSION

The screening results revealed that the compounds IV,IXa,XI,XII,XIII,XVI,XVII,XVIII have significantly antimicrobial activity ,however the compound XI is higher biologically active against gram +ve and gram –ve bacteria ,while compounds XIII,XVI exhibit strong activity against Basillus Subtilis and compounds XII,XVIII showed moderate to considerate to antibacterial activity against the most employed organisms , but the data indicate the compounds IV ,IXa,XVII is biologically inactive against gram +ve and gram –ve .

MATERIALS AND METHODS

Experimental

All melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Center, Cairo University.IR spectra (KBr) were recorded on a Bruker FTIR spectrophotometer and ¹H-NMR spectra were recorded in (DMSO - d₆ and CDCl₃) on Varian Gemini spectrophotometer at 200 MHz and Varian Mercury spectrophotometer at 300 MHz, using tetra methyl silan (TMS) as an internal reference . EIMS were performed at 70 ev with Shimadzu GCMS (QP1000 EX). Characterization and physical data for the synthesized compounds are listed in tables 3, 4.

4-(3, 4-Dimethyl-phenyl)-5, 6, 7, 8-tetrabromo-2H-phthalazin-1-one II:

A mixture of I (3.4g; 0.006mol) and hydrazine hydrate 98% (2.7 ml; 0.036 mol) in ethanol (50 ml) was refluxed for 3 hours. The reaction mixture was allowed to cool and the separated product was filtered and dried. Crystallization of the crude product from dioxane, afforded

(II). Yield 62 %, m.p.272 °C, Anal. Calcd. for $C_{16}H_{10}Br_4N_2O$, Calculated : C 33.96 , H 1.78 , Br 56.48 , N 4.95 , Found : C 33.91 ,H 1.75 ,Br 56.42 ,N 4.91. IR(KBr) cm^{-1} ,3309 (NH) , 3061 (CH,aromatic) , 2916 (CH,aliphatic) and 1706 (C=O) . 1H -NMR (200MHz,DMSO- d_6 δ) ppm. 2.34(s,6H,2Ar- CH_3), 7.45 (d,CH),7.57(s,CH) , 7.67(d,CH) and 7.2 (s, 1H, NH). Mass:m/z = M^+ 566 (81.3%) , $M^+ - H$ 565(100 %) ,551,537,511,496.

[4-(3, 4-Dimethyl-phenyl)-5, 6, 7, 8-tetrabromo-1-oxo-1H-phthalazin-2-yI]-acetyl chloride III:

A mixture of phthalazine (II)(1g), chloroacetyl chloride (5 ml) was refluxed for 2 hours on steam bath. The reaction mixture poured into water, and then the mixture was allowed to stand at room temperature overnight. The collected solid was filtered off, washed well with water and dried. Crystallization from Pet.-ether (80-100) afforded (III). Yield 98 %, m.p.240 °C , Anal. Calcd. for $C_{18}H_{11}Br_4ClN_2O_2$, Calculated : C 33.66, H 1.73, Br 49.76, N 4.36, Cl 5.52 , Found : C 33.61, H 1.70, Br 49.72, N 4.33, Cl 5.49 . IR(KBr) cm^{-1} , 1751&1685 (2C=O). 1HNMR (200MHz,DMSO- d_6 δ)2.34(s,6H,2Ar CH_3),4.75(s,2H, CH_2),7.45(d,CH),7.57, (s, CH) , and 7.67(d, CH).

[4-(3, 4-Dimethyl-phenyl)-5, 6, 7, 8-tetrabromo-1-oxo-1H-phthalazin-2-yI]-acetic acid hydrazide IV:

A mixture of the acid chloride (III) (6.4, 0.01mol.) and hydrazine hydrate (0.015 mol, 0.75ml) in ethanol (50 ml) was refluxed for 10 hours. The reaction mixture was allowed to cool and the separated product was filtered and dried. Crystallization of the crude product with benzene, afforded (IV). Yield 69% , m.p.220°C , Anal. Calcd.for $C_{18}H_{14}Br_4N_4O_2$. Calculated: C 33.89, H 2.21 ,Br 50.10, N 8.78, Found : C 33.83, H 2.30, Br 49.81, N 8.72 . IR(KBr) cm^{-1} 3263, 3312(NH and NH_2), 3021(CH, aromatic), 2916(CH, aliphatic) and1705(C=O). 1H -NMR (200MHz, DMSO- d_6 δ) 2.34 (s,6H,2Ar CH_3), 4.09(s,2H, CH_2), 4.22(2H, NH_2),7.45(d,CH),7.57(s, CH) , 7.67(d, CH) and 9.08(1H, NH). Mass :m/z = (M-Br) 553(100%), 133, 105 and 77 (48%).

N-Phenyl amino carbonyl [4-(3, 4-Dimethyl-phenyl)-5, 6, 7, 8-tetrabromo-1-oxo-1H-phthalazin-2-yI]-acetic acid hydrazide V:

A mixture of the hydrazide (IV) (6.39, 0.01mol) and phenylisocyanate (0.04 mol, 4.3 ml) in dry benzene (50 ml) was refluxed for 10 hours on steam bath. The excess solvent was evaporated and the reaction mixture was recrystallized from methanol, afforded (V). Yield 71% , m.p.170 °C , Anal. Calcd.for $C_{25}H_{19}Br_4N_5O_3$. Calculated : C 39.66 , H 2.53 , Br 42.22, N 9.25. Found : C 39.62 , H 2.50 ,Br 42.19 , N 9.22. IR(KBr) cm^{-1} 3299 (NH) and 1644 and 1711(2 C=O). 1HNMR (200MHz,DMSO- d_6 δ) 2.34 (s, 6H, two Ar- CH_3), 4.09(s,2H, CH_2) , 6.0 (s,1H, $NHNHCO$),7.45-7.67(m,8H,aromaticprotons), 9.26 (s,1H, $CONHC_6H_5$) and 10.08(s,1H, CH_2CONH).

[4-(3, 4-Dimethyl-phenyl)-5, 6, 7, 8-tetrabromo-1-oxo-1H-phthalazin-2-yI]-Acetic acid [1-methyl-3-oxo-butylidene]-hydrazide VI:

A mixture of the acetic acid hydrazide (IV) (1.9 g, 0.003mol.) and acetyl acetone (2ml) was heated in an oil bath at 160 °C for 8 hours .The fused mixture was then treated with ethanol and filtered. The crude product was crystallized from toluene. Yield 60% , m.p.190 °C , Anal. Calcd.for $C_{23}H_{20}Br_4N_4O_3$. Calculated : C 38.37 , H 2.80 , Br 44.39, N 7.78. Found : C 38.28 , H 2.81 ,Br 44.08 , N 7.71. IR(KBr) cm^{-1} 3127 (NH),1722, 1704 and 1669 (3C=O). 1HNMR (200MHz,DMSO- d_6 δ) 1.49 (s,3H, O=C CH_3), 2.25(s,3H, N=C- CH_3), 2.34 (s, 6H, two Ar- CH_3), 2.5(s,2H, CH_2COCH_3), 4.09(s,2H,N- CH_2 -CO), 7.45(d,CH), 7.57 (s,CH) , 7.67(d,CH) and 10.58(s,1H, NH).

Acetic acid N'-acetyl-2-(5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl)acetohydrazonic anhydride VII.

A mixture of the hydrazide (IV) (1.9g; 0.003mol) and acetic anhydride (10ml) was refluxed for 7 hours. After cooling, the reaction mixture was poured into water; the solid obtained was washed with water several times and crystallized from Petroleum ether/ ethanol. Yield 60 %, m.p.200 °C, Anal. Calcd. for $C_{22}H_{18}Br_4N_4O_4$, Calculated : C 36.60 , H 2.51 , Br 44.27 , N 7.76 , Found : C 36.58 , H 2.48 , Br 44.24 , N 7.78. IR(KBr) cm^{-1} 3288(NH) ,1675 (amide C=O) and 1741 (acetoxo C=O) . 1H NMR(200MHz,DMSO- d_6 δ) 2.04(s,3H, NHCO-CH₃), 2.12(s,3H,OCOCH₃) , 2.34 (s, 6H, two Ar-CH₃), 3.2(s,2H, CH₂), 7.45(d,CH), 7.57(s,CH), 7.67(d,CH), and 10.58(s,1H,NH).

5,6,7,8-Tetrabromo-4-(3,4-dimethylphenyl)-2-(2-(5-hydroxy-3-methyl-1H-pyrazol-1-yl)-2-oxoethyl)phthalazin-1(2H)-one VIII:

A mixture of the acetic acid hydrazide (IV) (0.6g; 0.001mol), ethyl aceto acetate (0.126 ml; 0.001mol) was refluxed in ethanol (20ml) for 12 hours. On cooling, the separated solid was filtered off and crystallized from dioxane. Yield 84 %, m.p.288 °C, Anal. Calcd. for $C_{22}H_{16}Br_4N_4O_3$, Calculated : C 37.53 , H 2.29 , Br 45.40 , N 7.96 , Found : C 37.48 , H 2.23 , Br 45.34 , N 7.91. IR(KBr) cm^{-1} 3227(OH),1722and 1665 (2 C=O) , 1H NMR(200MHz,DMSO- d_6 δ) 2.30(s,3H, CH₃), 2.34 (s, 6H, two Ar-CH₃) , 4.31(s,2H, CH₂), 6.1(s,1H, CH), 7.45(d,CH), 7.57(s,CH) , 7.67(d,CH), and 11.40(s,1H,OH).

[4-(3, 4-Dimethyl-phenyl)-5, 6, 7, 8-tetrabromo -1-oxo-2H-phthalazin-2-yl]- Acetic acid [(1-aryl) methylidene]- hydrazide IXa-d:

A mixture of the acetic acid hydrazide (IV) (6.34; 0.01mol), the appropriate aromatic aldehyde, namely, anisaldehyde, furfural, 4-chloro-benzaldehyde and piperonal (0.01 mol.) and few drops of piperidine was refluxed in boiling ethanol (20 ml) for 12 hours. After cooling, the collected solid crystallized from the proper solvent

IXa : Crystallization from dioxane, Yield 71 %, m.p.170 °C, Anal. Calcd. for $C_{26}H_{20}Br_4N_4O_3$, Calculated : C 41.30 , H 2.67 , Br 42.27 , N 7.41 , Found : C 41.23 , H 2.66 , Br 41.98 , N 7.36. IR(KBr) cm^{-1} 3303 (NH) and 1704 (C=O). 1H NMR(200MHz,DMSO- d_6 δ) 2.34(s, 6H, two Ar-CH₃) , 3.83(s,3H,OCOCH₃), 4.14 (s,2H,NCH₂CO), 7.06-7.84 (m, 7H, aromatic protons) , 8.51(s, 1H, N= CH-Ar) and 10.8 (s,1H,NH) .

IXb : Crystallization from ethanol ,Yield 79 %, m.p.280 °C, Anal. Calcd. for $C_{23}H_{16}Br_4N_4O_3$, Calculated : C 38.58 , H 2.25 , Br 44.64 , N 7.82 , Found : C 38.41 , H 2.22 , Br 44.59 , N 7.80. IR(KBr) cm^{-1} 3133 (NH) and 1696 (C=O).Mass m/z= M^+ 704(4.02%)and 583(100%).

IXc : Crystallization from ethanol ,Yield 85 %, m.p.194 °C, Anal. Calcd. for $C_{25}H_{17}Br_4ClN_4O_2$, Calculated : C 39.48 , H 2.25 , Br 42.03 , N 7.37 , Cl 4.66 , Found : C 39.34 , H 2.22 , Br 41.90 , N 7.32, Cl 4.62 , IR(KBr) cm^{-1} 3207 (NH) and 1659 (C=O). 1H NMR(200MHz,DMSO- d_6 δ) 2.34(s, 6H, two Ar-CH₃) ,4.14(s,2H,NCH₂CO), 7.45-7.90 (m, 7H, aromatic protons) , 8.46(s, 1H, N= CH-Ar) and 10.5 (s,1H,NH) . Mass m/z= M^+ 760 (3.2%) and 583 (100%).

IXd : Crystallization from ethanol ,Yield 82 %, m.p.198 °C, Anal. Calcd. for $C_{26}H_{18}Br_4N_4O_4$, Calculated : C 40.55 , H 2.36 , Br 41.51 , N 7.28 , Found : C 40.40 , H 2.25 , Br 41.35 , N 7.12. IR(KBr) cm^{-1} 3190 (NH) and 1650 (C=O). 1H NMR(200MHz,DMSO- d_6 δ) 2.34(s, 6H, two Ar-CH₃), 4.09(s, 2H, NCH₂CO), 7.45-7.77 (m, 6H, aromatic protons) , 8.54(s, 1H, N= CH-Ar) and 11.07 (s,1H,NH)

N'-(4-Methoxybenzyl)-N'-(phenylthio)-2-(5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl)acetohydrazide X :

A mixture of the benzylidene derivative (**IXa**) (0.75 g; 0.001 mol), thiophenol (0.165g; 0.0015mol) and anhydrous aluminum chloride (0.5g) was refluxed in dry DMF (20 ml) and three drops of piperidine for 20 hours. The reaction mixture was then poured into water and the precipitated solid was filtered. The residue was washed with water then with hot ethanol. The crude product was crystallized from dioxane. Yield 43 %, m.p.300 °C, Anal. Calcd. for $C_{32}H_{26}Br_4N_4O_2S$, Calculated : C 44.73 , H 3.03 , Br 36.90 , N 6.47 , S 3.70 , Found : C 44.59 ,H 3.18 ,Br 37.06 ,N 6.28 , S 3.73 IR(KBr) cm^{-1} 3170 (NH), 1673 and 1722(2C=O). 1H NMR(200MHz,DMSO- d_6 δ) 2.0 (s, 1H, NH amine),2.34 (s, 6H , two Ar- $\underline{CH_3}$), 3.83 (s,3H,O- $\underline{CH_3}$) , 4.09 (s,2H,N $\underline{CH_2}$ CO) , 4.95 (s, 1H, NH- \underline{CH} -S) , 6.87-7.67(m,12H,aromatic protons) and 8 (s, 1H, NH Sec. amide).

[4-(3, 4-Dimethyl-phenyl) -5, 6, 7, 8-tetrabromo-1-oxo -1H-phthalazin - 2-yl]- N-(4-oxo-2anisyl- thiazolidin -3- yl)-acetamide XI:

A mixture of (**IXa**) (0.75 g; 0.001mol), thioglycolic acid (0.165g; 0.0015mol), and anhydrous aluminum chloride (0.5g) was refluxed in dry DMF (20 ml) and three drops of piperidine for 20 hours under a calcium chloride guard tube. The reaction mixture was then poured into water and the precipitated solid was filtered. The residue was washed with water then with hot ethanol. The crude product was crystallized from Pet.-ether (80-100). Yield 65 %, m.p.213 °C, Anal. Calcd. for $C_{28}H_{22}Br_4N_4O_4S$, Calculated : C 40.51 , H 2.67 , Br 38.50 , N 6.75 , S 3.86 , Found : C 40.50 ,H 2.60 ,Br 38.55 ,N 6.81 , S 3.81, IR(KBr) cm^{-1} 3263 (NH), 3004 (CH aromatic), 2918 & 2854 (CH aliphatic), and 1680 (C=O). 1H NMR(200MHz,DMSO- d_6 δ) 2.34 (s, 6H , two Ar- $\underline{CH_3}$), 3.38(s,3H,O- $\underline{CH_3}$) , 3.95(s, 2H,CO- $\underline{CH_2}$ -S) , 4.09 (s,2H,N $\underline{CH_2}$ CO) , 5.92 (s, 1H, CH-S) .5.59 (s,1H, N-CH-Ar) , 7.26-7.67(m,8H,aromatic protons) and 8 (s, 1H, NH).

N-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetid-1-yl)-2-(5, 6, 7, 8-tetrabromo-4-(3, 4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl) acetamide XII:

A mixture of the benzylidene derivative (**IXa**) (1.5 g; 0.002mol), triethyl amine (0.84 ml; 0.006mol) was dissolved in dry benzene or dry dioxane. Add chloroacetyl chloride (0.64 ml; 0.008mol) drop wisely to the reaction mixture with stirring through 1/2 hr. complete stirring for 3 hrs.The-precipitated solid was filtered, washed with dry benzene or dioxane. Concentrate the filtrate then pour in petridish. Recrystallize the formed solid from Pet.-ether (80-100). Yield 67 %, m.p.142 °C, Anal. Calcd.for $C_{28}H_{21}Br_4ClN_4O_4$, Calculated : C 40.39 ,H 2.54, Br 38.39, N 6.73 , Cl 4.26 Found : C 40.35 ,H 2.50 ,Br 38.34 , N 6.71 , Cl 4.21 , IR(KBr) cm^{-1} 3183 (NH), 1701 and1687 (2C=O). 1H NMR(200MHz,DMSO- d_6 δ) 2.34 (s, 6H , two Ar- $\underline{CH_3}$), 3.38(s,3H,O- $\underline{CH_3}$) , 4.13(s,2H,N $\underline{CH_2}$ CO) , 5.0(d, 1H, \underline{CH} -Ar propiolactam), 5.45(d, 1H, \underline{CH} -Cl propiolactam), 6.34-7.67(m,7H,aromatic protons) and 8 (s, 1H, NH). Mass: m/z = M^+ 832 (1%) and 77 (100%).

Ammonium 2-(2-(5, 6, 7, 8-tetrabromo-4-(3, 4-dimethylphenyl)-1-oxo phthalazin -2(1H)-yl) acetyl) hydrazinecarbodithioate XIII:

To a solution of the hydrazide compound (**IV**) (0.01 mole, 6.34 g), in ammonium hydroxide (40 ml), 2 ml of carbon disulfide was added drop wise; and left overnight, the solid product formed was filtered off and recrystallized from Pet.-ether (80-100) to give (**XIII**). Yield 52 %, m.p.196 °C, Anal. Calcd. for $C_{20}H_{18}Br_4N_6O_3S_2$, Calculated : C 31.03 , H 2.34 , Br 41.29 , N 10.86 ,S 8.28 Found : C 31.10 ,H 2.31 ,Br 41.50 ,N 10.52, S 8.60, IR(KBr) cm^{-1} 3423 (NH), 3080(CH, aromatic), 2915(CH, aliphatic), 1708, 1688 (2 C=O) and 1267 (C=S). 1H NMR(200MHz,DMSO- d_6 δ)2.3(1H,NH

amine), 2.34(s, 6H, 2ArCH₃), 4.15(s, 2H, CH₂), 4.22(2H, NH₂), 7.45(d, CH), 7.57(s, CH), 7.67(d, CH) and 10.08(1H, NH Sec. amide). Mass: m/z = (M⁺) 729(1.6%) and (M⁺ - S) (1.4%).

Methyl 2-(2-(5, 6, 7, 8-tetrabromo-4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl) acetyl) hydrazine carbodithioate XIV:

To a solution of dithiocarbamate compound (XIII) (7.27 g, 0.01 moles), in DMF (30 ml), (0.93 ml, 0.015 mole) of methyl iodide was added, the reaction mixture was refluxed for 7 hours. Then cooled reaction and poured into ice - cold water, then the separated solid was filtered off, washed well with water and dried. Recrystallization from dioxane, afforded (XIV). Yield 90 %, m.p. 298 °C, Anal. Calcd. for C₂₀H₁₆Br₄N₄O₂S₂, Calculated : C 32.99, H 2.21, Br 43.90, N 7.69, S 8.81, Found : C 32.96, H 2.20, Br 43.93, N 7.66, S 8.79, IR(KBr)cm⁻¹ 3291 (NH), 3080 (CH, aromatic), 2920 & 2949 (CH, aliphatic), 1709 (C=O) and 1258 (C=S). ¹H NMR (200 MHz, DMSO-d₆) 2.0 (1H, NH amine), 2.34 (s, 6H, 2ArCH₃), 2.55 (s, 3H, S-CH₃), 4.10 (s, 2H, CH₂), 7.45 (d, CH), 7.57 (s, CH), 7.67 (d, CH) and 10.0 (1H, NH Sec. amide).

Dimethyl 2-(5, 6, 7, 8-tetrabromo-4-(3, 4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl) acetyl carbonohydrazonodithioate XV:

To a solution of dithiocarbamate compound (XIII) (7.27 g, 0.01 moles), in DMF (30 ml), (1.9 ml, 0.03 mole) of methyl iodide was added, the reaction mixture was refluxed for 7 hours. Then cooled reaction and poured into ice - water, then the separated solid was filtered off, washed well with water and dried. Recrystallization from dioxane, afforded (XV). Yield 83 %, m.p. 347 °C, Anal. Calcd. for C₂₁H₁₈Br₄N₄O₂S₂, Calculated : C 33.99, H 2.44, Br 43.07, N 7.55, S 8.64, Found : C 33.96, H 2.40, Br 43.03, N 7.56, S 8.69, IR(KBr)cm⁻¹ 3214 (NH), 3056 (CH, aromatic), 2924 & 2943 (CH, aliphatic) and 1675 (C=O).

N-(4-Oxo-2-thioxo-1,2-dihydroquinazolin-3(4H)-yl)-2-(5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl)acetamide XVI:

A mixture of monomethyl compound (XIV) (7.42 g, 0.01 mole), in DMF (30 ml) and (1.37 gm, 0.01 mole) of anthranilic acid was refluxed for 6 hours. Then cool, concentrate, the separated solid was filtered off, washed well with water and dried. Recrystallization from the ethanol, afforded (XVI). Yield 47 %, m.p. 244 °C, Anal. Calcd. for C₂₆H₁₇Br₄N₅O₃S, Calculated : C 39.08, H 2.14, Br 40.00, N 8.76, S 4.01, Found : C 39.02, H 2.10, Br 40.05, N 8.79, S 4.04, IR(KBr)cm⁻¹ 3210 (NH), 3023 & 3072 (CH, aromatic), 2924 (CH, aliphatic) and 1663 (C=O). ¹H NMR (200 MHz, DMSO-d₆) 2.34 (s, 6H, 2ArCH₃), 4.0 (1H, C-NH aromatic), 4.9 (s, 2H, CH₂), 6.99-7.67 (m, 7H, aromatic protons) and 10.0 (1H, NH Sec. amide).

N'-(4-oxo-1H-benzo[d][1,3]oxazin-2(4H)-ylidene)-2-(5,6,7,8-tetrabromo-4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl) acetohydrazide XVII:

A mixture of dimethyl compound (XV) (7.56 g, 0.01 mole), in DMF (30 ml) and (1.37 gm, 0.01 mole) of anthranilic acid. Then 0.01 mole of potassium hydroxide in 2 ml water was added to the reaction mixture. Reflux for 5 hours, then cool, concentrate, the separated solid was filtered off, washed well with water and dried. Recrystallization from acetic acid, afforded (XVII). Yield 56 %, m.p. 300 °C, Anal. Calcd. for C₂₆H₁₇Br₄N₅O₄, Calculated : C 39.88, H 2.19, Br 40.82, N 8.94, Found : C 39.84, H 2.15, Br 40.80, N 8.90, 3330 & 3252 (NH), 3057 (CH, aromatic), 2929 (CH, aliphatic) and 1658 (C=O).

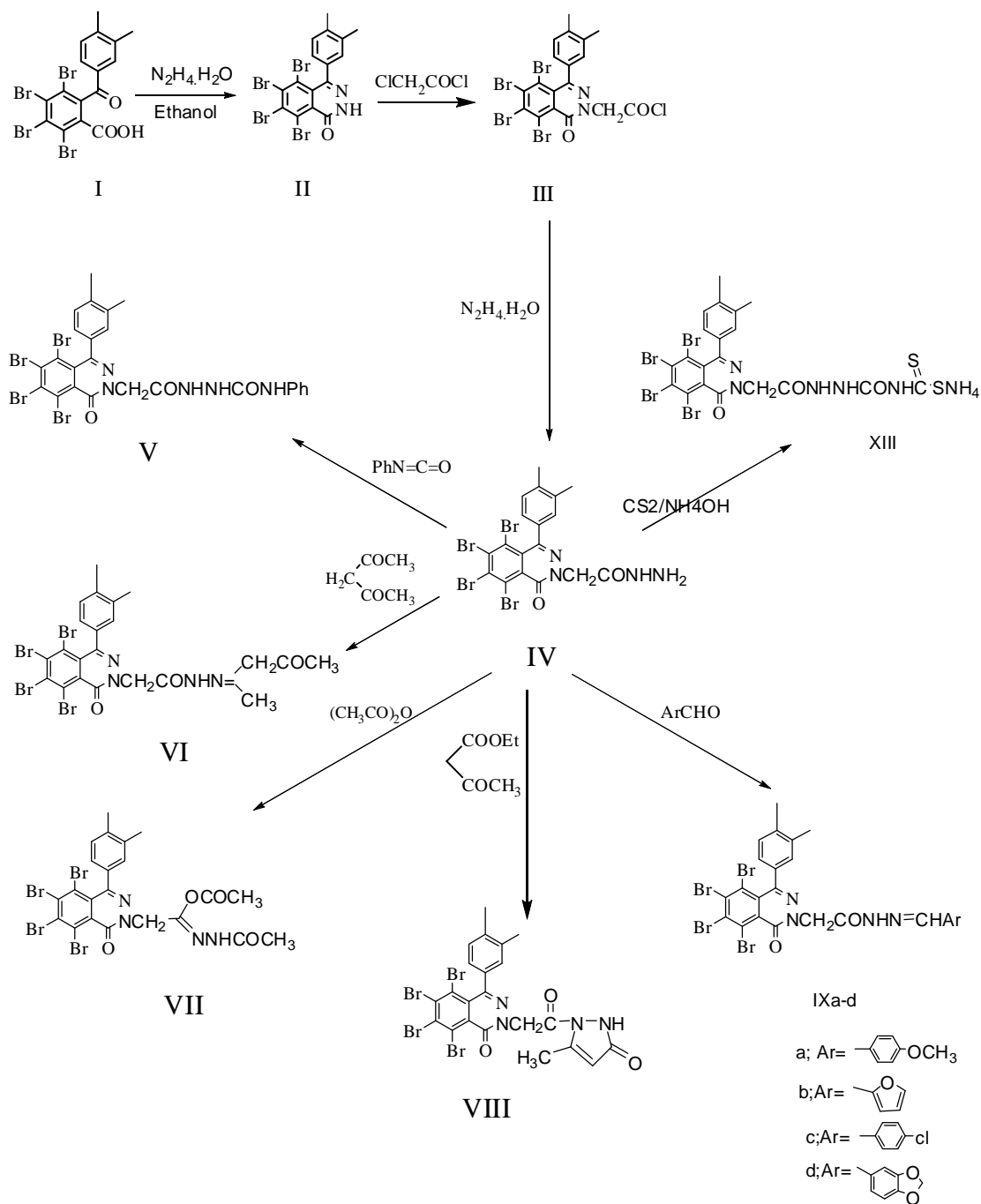
N-(4-oxo-2-thioxothiazolidin-3-yl)-2-(5, 6, 7, 8-tetrabromo-4-(3, 4-dimethyl phenyl)-1-oxophthalazin-2(1H)-yl) acetamide XVIII:

To an aqueous solution of sodium chloroacetate (0.01 mole, 7.27 g, 0.01 mole) dithiocarbamate compound (XIII) was added portion wise during 10 minute with stirring. The stirring was continued at room temperature for 3 hrs. Then a hot solution of concentrated hydrochloric acid (66 ml) and water (26 ml) was added. On cooling a precipitate was formed which was filtered off and recrystallized from ethanol, afforded (XVIII). Yield 42 %, m.p. 199 °C, Anal. Calcd. for C₂₁H₁₄Br₄N₄O₃S₂, Calculated : C 33.45, H 1.87, Br 42.38, N 7.43, S 8.50, Found : C 33.22, H 1.74, Br 42.02, N 7.30, S 8.77. IR(KBr)cm⁻¹ 3323 (NH), 3080(CH, aromatic), 2857 & 2925 (CH, aliphatic), 1714 (C=O) and 1255 (C=S). ¹H NMR(200MHz, DMSO-d₆ δ) 2.34(s, 6H, 2ArCH₃), 4.11 (s, 2H, SCH₂), 4.3(s, 2H, CH₂), 7.45-7.67(m, 3H, aromatic protons) and 10.9(1H, NH Sec. amide).

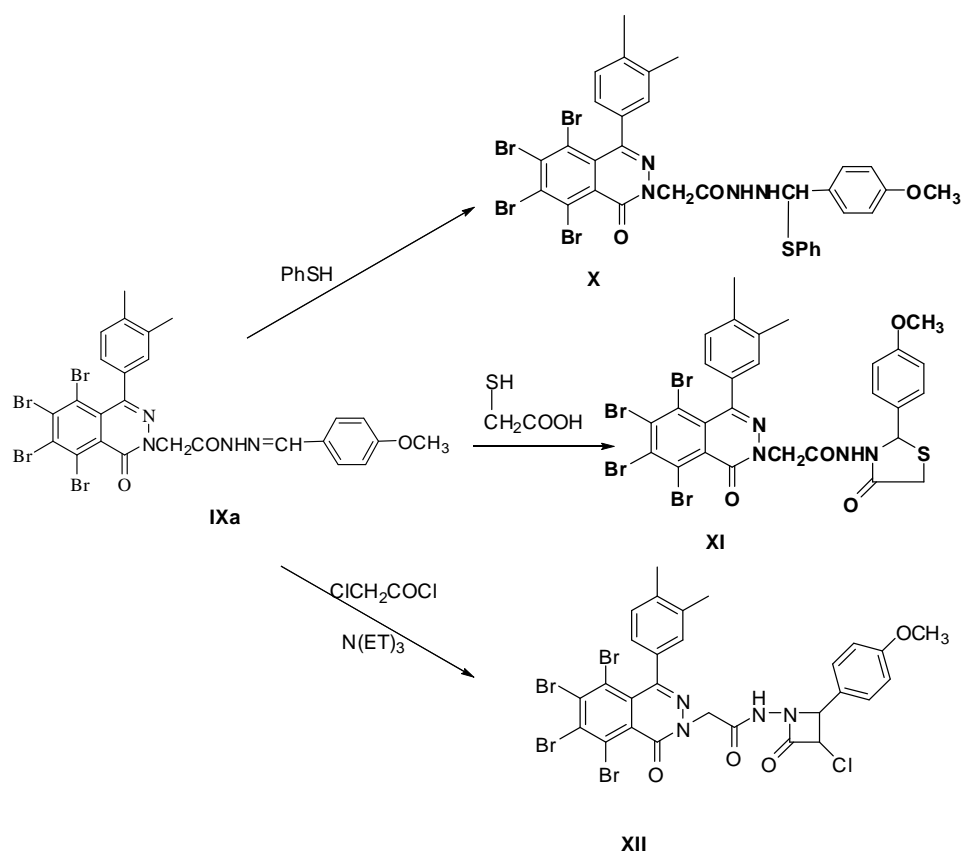
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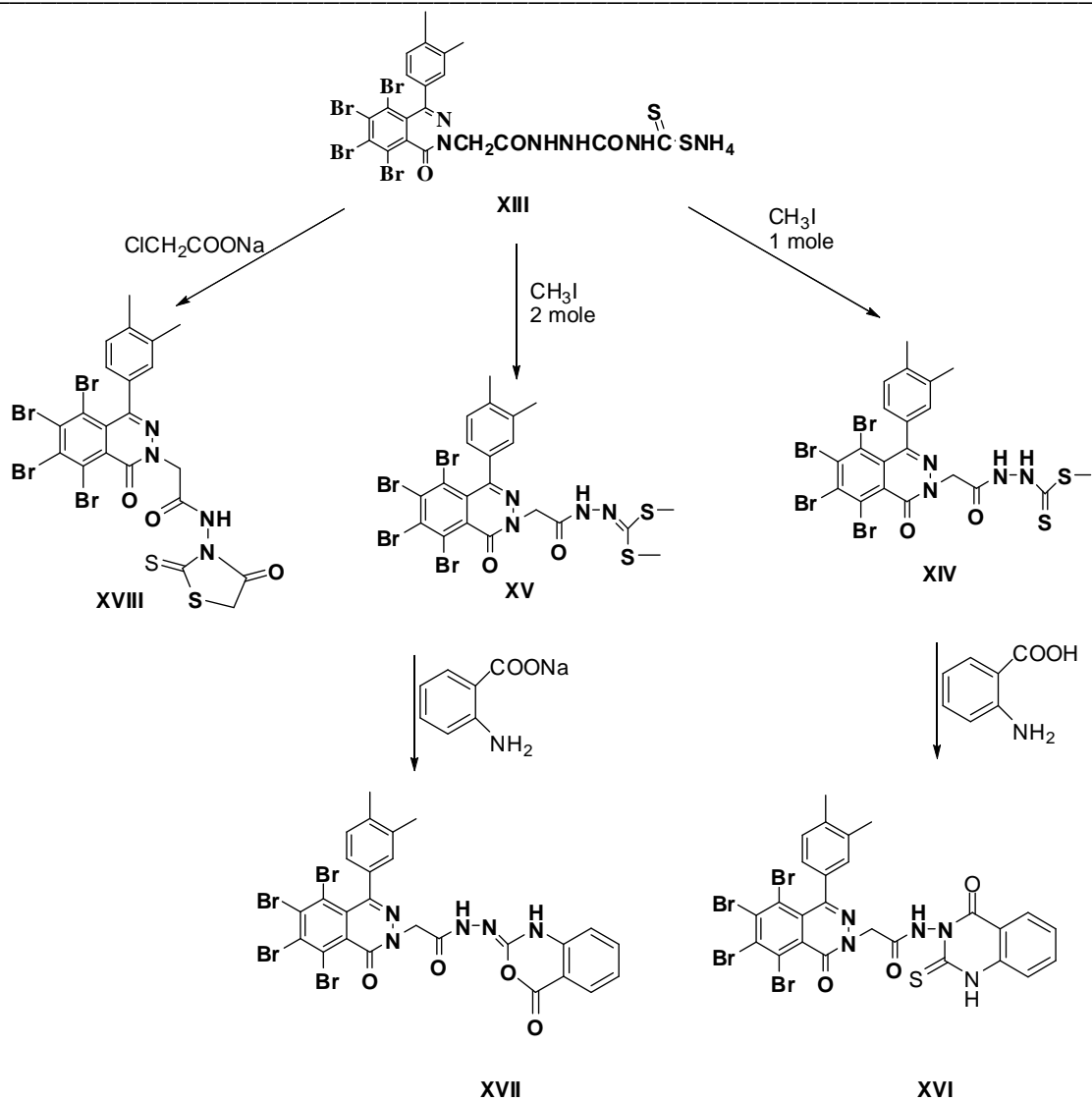
Scheme for synthesis



Scheme 1



Scheme 2



Scheme 3