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DESIGN, SYNTHESIS AND MOLECULAR MODELING OF CERTAIN IMIDAZO AND OXAZOLOPYRIDINE DERIVATIVES OF BIOLOGICAL INTEREST

Eman K.A. Abdelall*, Osama M. El -Badry; Sameha M. A. Roshdy and Mervat M. El – Enany
Organic Chemistry Department, Faculty of Pharmacy, Cairo University, Cairo
* Organic Chemistry Department, Faculty of Pharmacy, Beni Sueif University, Beni Sueif , Egypt

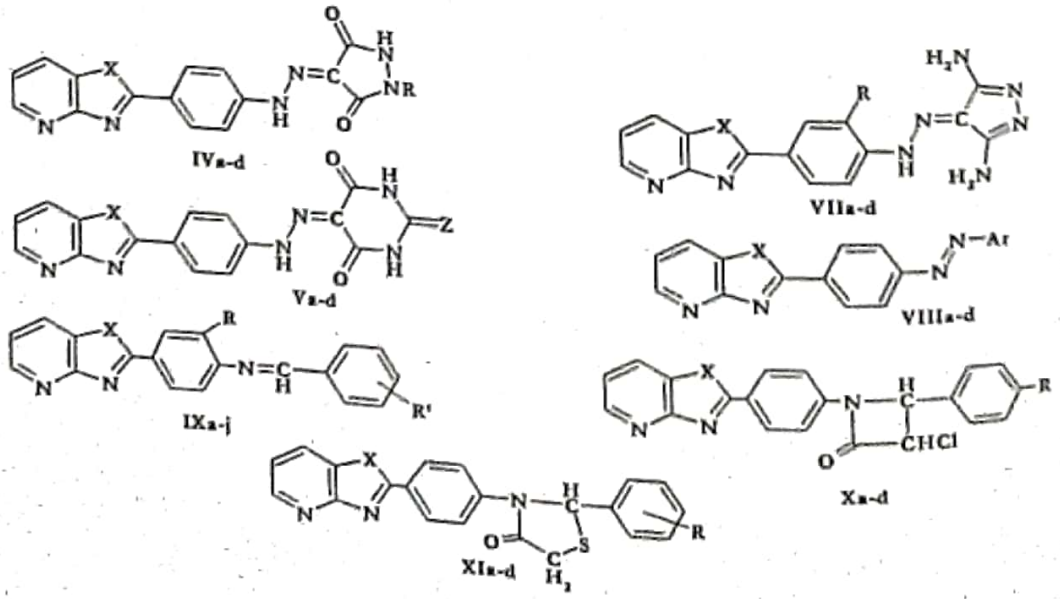
ABSTRACT:

2-(4- Amino-3-subsituted and unsubsituted phenyl) imidazo and/or oxazolo)[4,5-*b*]pyridines **Ia-h** were diazotized to afford **II** . Coupling of the latter with diethylmalonate afforded **IIIa,b** while its coupling with malononitrile afforded **VIa-d** the pyrazolo derivatives **IVa-d**, the pyrimido derivatives **IVa-d** were obtained when **IIIa,b** were cyclized with hydrazine, phenyl hydrazine , urea and thiourea respectively. The aminopyrazolo derivatives **VIIa-d** were obtained by cyclization of **VIa-d** with hydrazine. In addition a number of azo dyes were also synthesized. Another series of schiff,s bases were prepared from the reaction of **Ia-h** with different substituted benzaldhydes , then a novel series of cyclized compounds **Xa-d** and **XIa-d** were obtained by reaction of certain azomethine with chloroacetyl chloride and mercaptoacetic acid respectively. Molecular modeling and antimicrobial activity for some of the synthesized compounds were also involved.

INTRODUCTION

Imidazo and oxazolopyridine ring systems are of great importance in modern drug discovery hence they are considered as deaza analogues of the biologically important purine bases. Literature survey illustrated that many imidazo and oxazolo[4,5-*b*] pyridines possess a wide range of biological activities e.g. antimicrobial [1-5], antiviral [6,7], antihypertensive [8-11] and anti-inflammatory[12,13] activities. In addition, pyrazoles and pyrimidines receive a great attantion in literatures for their exciting biological importance and their roles as pharmacophores of considerable historical importance[14-18] Also, many azo compounds have been utilized in non textile applications such as pharmaceutical, biodegradable agrochemicals, and photographic technology[17]In addition significant antimicrobial activity of a number of azomethines[19,20] , thiazolidinones [21,22] and β-lactam[23,24] containing derivatives were also reported.

From this point of view and as a continuation of previous work[25,] some imidazo and oxazolopyridines **(IVa-d, Va-d, VIIa-d, VIIIa-k,IXa-v, Xa-d and XIa-d)** showing these pharmacophoric moieties were prepared.



RESULTS AND DISCUSSION

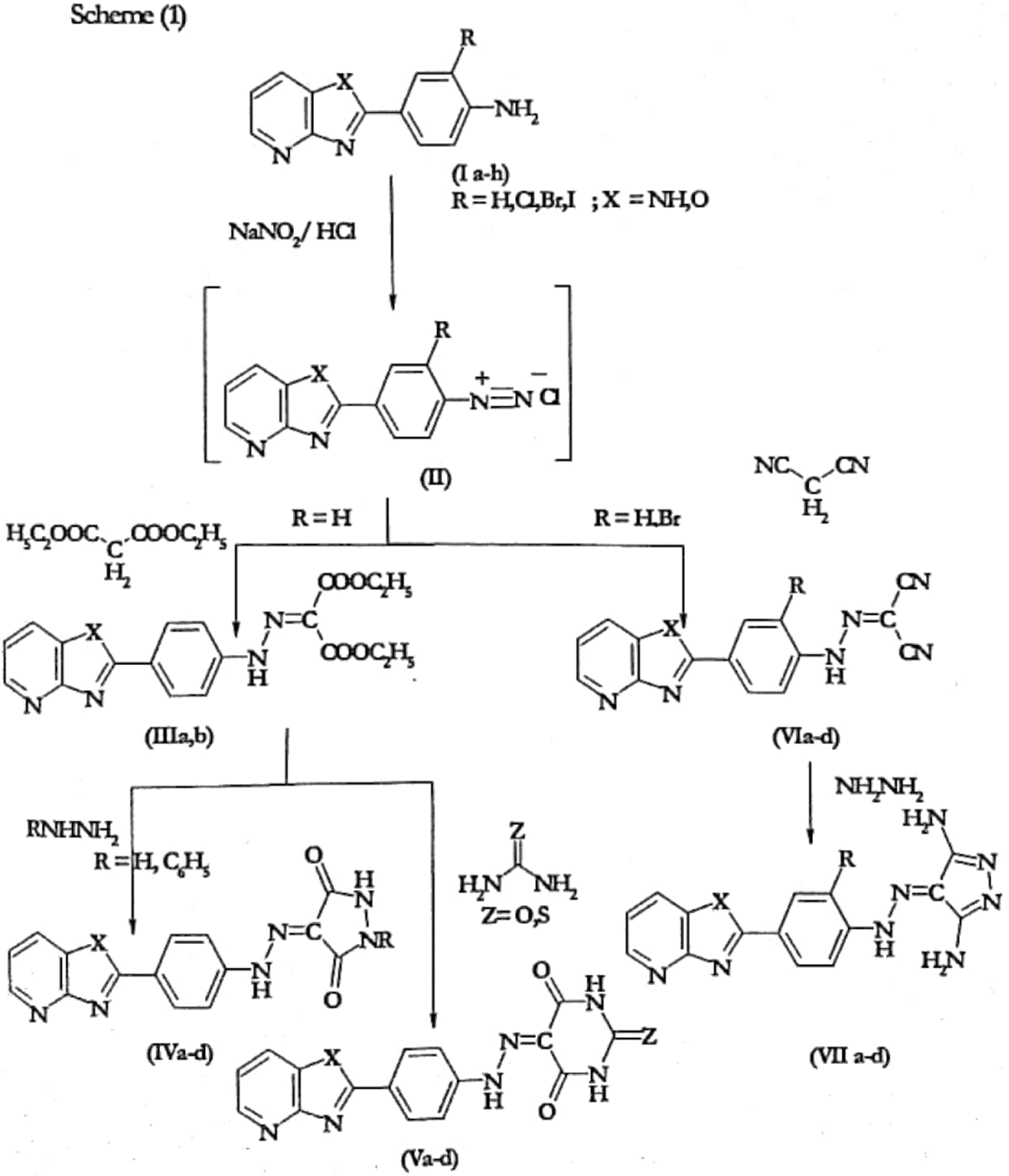
2-(4- Amino-3-subsituted and or unsubsituted phenyl) imidazo and/or oxazolo)[4,5-*b*]pyridines **Ia-h** [25,26] were prepared and diazotized by using sodium nitrite and hydrochloric acid to afford the corresponding diazonium salts **II**. Some of these diazonium salts **II** (R= H) were coupled with diethylmalonate in prescence of sodium acetate to afforded the diester derivatives **IIIa,b**. the latter were further cyclized with hydrazine derivatives to get the pyrazoldiones **IVa-d**. When, the diester derivatives **IIIa,b** were cyclized with urea and thiourea furnished the pyrimido derivatives **Va-d**. In a way to obtain the

aminopyrazoles **VIIa-d**, the diazonium salts **II** (R= H,Br) were coupled with malononitrile to get the dicyano derivatives **VIa-d** that were cyclized with hydrazine giving the target copmpounds **VIIa-d** (scheme I) The structures of all compounds were confirmed by elemental and spectral analyses.

. Further more, the diazonium salts **II** (R= H,Cl,Br,I) were coupled with different phenols[27] giving several dyes **VIIIa-k** (scheme II). In addition, a series of schiff's bases **IXa-v** were prepared by reaction of **Ia-h** with different substituted benzaldehydes in ethanol and in presence of a catalytic amount of acetic acid to improve the solubility of reactant in ethanol. The structures of compounds **IXa-v** were confirmed by elemental and spectral analyses.

Further, reaction of some of azomethine derivatives (**IX d,g,o and r**) with chloroacetyl chloride in presence of triethyl amine afforded the azitidinones **Xa-d** while Heating of **IXf,g,o and p** with mercaptoacetic acid in benzene for several hours afforded the thiazolidinones **XIa-d**(scheme III).

Scheme (1)



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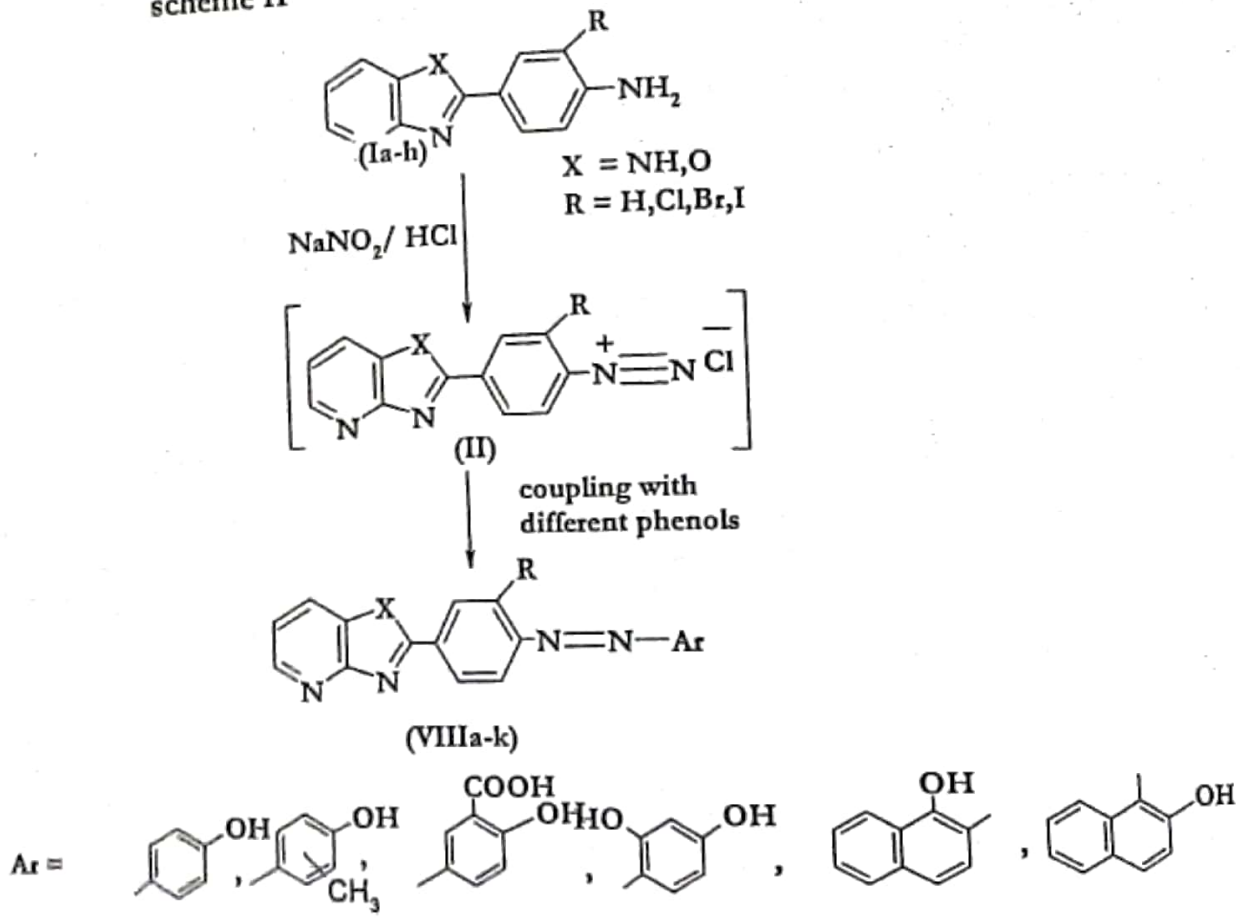
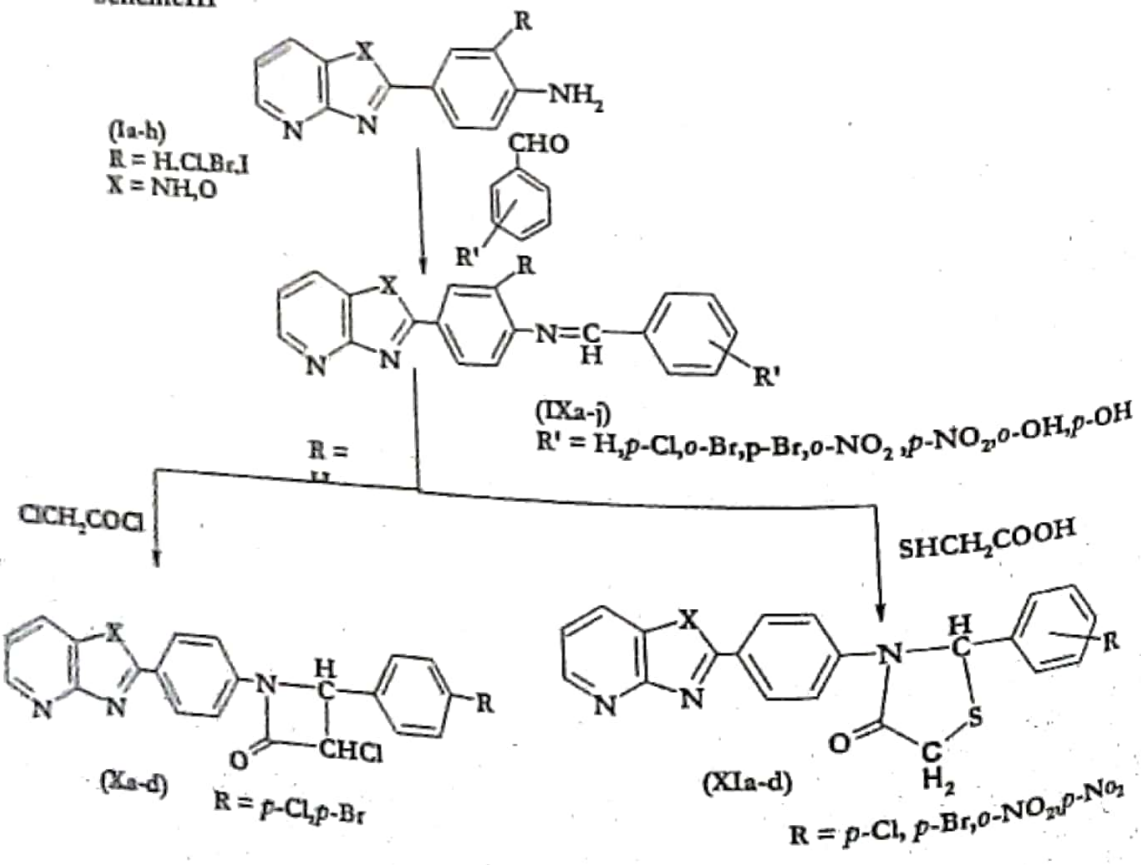
scheme II



SchemeIII



EXPERIMENTAL

Melting points were taken on a Griffin apparatus and were uncorrected. The IR spectra (KBr disks) were determined on Shimadzu IR435 spectrophotometer. ^{1}HNMR spectra were carried out on Varian Gemini 200 MHZ using TMS as internal slandered. Mass spectra were run on Shimadzu-GC MS QP1000. Progress of reactions was monitored by TLC using TLC sheets precoated with UV fluorescent silica gel Merck60 F254 that visualized using UV lamp and iodine vapor. The solvent used in TLC was chloroform/methanol (9.1or 9.5-0.5). Microanalyses were performed in the Micro analytical center Cairo University. Molecular modeling of some of the synthesized compounds was carried out at Faculty of Pharmacy, Ein-Shams University. The antimicrobial activity of selected compounds was operated in Microbiology Department, Cairo University. Diazonium salts were prepared as reported [28].

General procedure for 2-{4-[N^2 (Bis (ethoxy-carbonyl) methylene) hydrazino] phenyl}I midazo (or oxazolo)[4,5-*b*]pyridines III a or b

A solution of the corresponding diazonium salt of IIa (x= NH, R= H)or b(X =O, R=H)(0.01mol) was added step-wise to a solution of diethylmalonate (1.60 g, 0.01mol) in ethanol (30 ml) containing sodium acetate trihydrate (1.5g, 0.011 mol) with stirring and cooling. The reaction mixture was kept in ice for 2 h and filtered. The separated solid product was washed, dried and crystallized.

Compound **IIIa**(X=NH,R=H) : yield,80%,mp>300 °C, analysis ($C_{19}H_{19}N_5O_4$)calc C 59.84 H 5.02,N 18.36, found 59.66,5.34,18.52

(I.R: KBr cm $^{-1}$) Str.: for IIIa : 3550-3250 (NH), 1700 (C=O), 1640 (C=N imidazo moiety), 1620(C=N pyridine moiety).

^{1}HNMR (DMSO,δ-ppm) for IIIa: 1.29 (t ,6H, $2CH_3$); 4.3 (q, 4H, $2CH_2$);7.21(t, 1H, imidazopyridine C6-H); 7.54 (d, 2H, phenyl C2-H and C6-H); 8 (d, 1H, imidazopyridine C7-H); 8.24(d, 2H, phenyl C3-H and C5-H); 8.3 (d, 1H, imidazopyridine C5-H); 12.01 (s, IH, HN-N=C, D_2O exchangeable); 13.2 (s,1H,imidazopyridine NH, D_2O exchangeable).

EIMS (m/z) forIIIa: M/z (%): 382 $(M+1)^{+\cdot}$ (10.5), 381$(M)^{+\cdot}$ (56.8).

Compound **IIIb**(x=O,R=H): yield:82 mp241-243 °C, analysis $C_{19}H_{18}N_4O_5$cal C 59.69,H 4.74, N 14.65 found59.70,4.60,14.30.

General procedure for 2-{4-[N^2-(3,5-Dioxopyrazo-lidin-4-ylidene) hydrazino] phenyl} imidazo (or oxazolo) [4,5-*b*]pyridines IVa-d.

To a solution of the ester derivative IIIa (x= NH, R= H)or b(X =O, R=H) (0.01mol) in ethanol (20ml), hydrazine or phenyl hydrazine (0.01mol) was added and heated under reflux for 0.5 h (in case of phenyl hydrazine the reflux time was increased to 3h and a catalytic amount of sodium ethoxide was added). The reaction mixture was evaporated under vacuum and the residue left was washed with water, dried and crystallized (Table 1).

Table1:2-{4-[N^2-(3,5-Dioxopyrazo-lidin-4-ylidene)hydrazino] phenyl} imidazo (or oxazolo) [4,5-*b*]pyridines IVa-d.

IV	X	R	m.p.(°C) Solv. of cryst. Yield (%)	Mol. Form. (mol. wt.)	Analysis %	
					Calcd.	Found
a	NH	H	>300 DMF/MeOH 67	$C_{15}H_{11}N_7O_2$ 321.29	C 56.08 H 3.45 N 30.52	56.32 3.30 30.89
b	NH	C_6H_5	>300 DMF/MeOH 69	$C_{21}H_{15}N_7O_2$ 397.39	C 63.47 H 3.80 N 24.67	63.00 3.90 24.90
c	O	H	278-280 DMF 72	$C_{15}H_{10}N_6O_3$ 322.27	C 55.91 H 3.13 N 26.08	55.87 2.95 26.32
d	O	C_6H_5	285-288 DMF 66	$C_{21}H_{14}N_6O_3$ 398.36	C 63.31 H 3.54 N 21.10	63.44 3.79 21.58

(I.R: KBr cm $^{-1}$) Str: for IVa : 3540-3350 (NH), 1690 (C=O), 1637 (C=N imidazo), 1617 (C=N pyridine moiety).
^{1}H-NMR (DMSO,δ-ppm) for IVa 3.46 (s, 2H, 2NH of dioxopyrazolidine moiety, D_2O exchangeable); 7.29(t, 1H, imidazopyridine C6-H); 7.84-7.97 (m,, 3H, imidazopyridine C7-H, phenyl C3-H and C5-H); 8.37-8.45 (m, 3H, phenyl C2-H and C6-H and imidazopyridine C5-H); 12.1 (s, 1H, HN-N=C, D_2O exchangeable); 13.6 (s, IH, imidazopyridine NH, D_2O exchangeable) .

EIMS (m/z) for IVa: M/z (%): 322 $(M+1)^{+\cdot}$ (5.6), 321$(M)^{+\cdot}$ (14.5).

General procedure for compounds Va-d;2-{4-[N²-(2,4,6-Trioxoperhydropyrimidin-5-ylidene) hydrazino] phenyl} imidazo (or oxazolo) [4,5-*b*]pyridines Va,c and 2-{4-[N²-(4,6-Dioxo-2-thioxoperhydropyrimidin-5-ylidene) hydrazino] phenyl} imidazo(or oxazolo)[4,5-*b*]pyridines Vb,d.

The ester derivative IIIa or IIIb (0.01 mol) was added to an ethanolic solution of equimolar sodium ethoxide then a solution of dry urea or thiourea (0.01mol) in ethanol (30 ml). After shaking well, the reaction mixture was heated under reflux for 7h in an oil bath at 110 °C. After cooling, the reaction mixture was treated with hot water (10ml) then with concentrated hydrochloric acid (1ml) until become acidic to litmus paper(pH = 4.5). The resulting solution was filtered, washed with water, dried and crystallized (Table 2).

Table 2: 2-{4-[N²-(2,4,6-Trioxoperhydropyrimidin-5-ylidene) hydrazino] phenyl} imidazo (or oxazolo) [4,5-*b*]pyridines Va,c and 2-{4-[N²-(4,6-Dioxo-2-thioxoperhydropyrimidin-5-ylidene) hydrazino] phenyl} imidazo(or oxazolo)[4,5-*b*]pyridines Vb,d.

V	X	Z	m.p.(°C) solvent of cryst. yield	Mol. Form. (mol. wt.)	Analysis %	
					Calcd.	Found
a	NH	O	>300 Dioxan/ EtOH 66	$C_{16}H_{11}N_7O_3$ 349.29	C 55.02 H 3.17 N 28.07	55.42 3.33 28.21
b	NH	S	>300 Dioxan/ EtOH 63	$C_{16}H_{11}N_7O_2S$ 365.36	C52.60 H.3.04 N 26.84	52.69 3.40 26.90
c	O	O	278-280 DMF/EtOH 65	$C_{16}H_{10}N_5O_4$ 350.26	C 57.15 H 3.00 N 20.83	57.47 2.99 20.53
d	O	S	285-288 DMF/ EtOH 65	$C_{16}H_{10}N_6O_3S$ 366.34	C 52.46 H 2.75 N 22.94	52.99 2.50 22.85

(I.R: KBr cm^{-1}) Str.: for Vd :3600 -3200 (NH), 1700 (C=O), 1630-1610 (C=N, oxazolo and pyridine moieties)
^{1}H-NMR (DMSO,δ-ppm) for Vd:4.1 (s,2H,2NH of perhydropyrmidine moiety, D_2O exchangeable); 7.34 (t,1H, oxazolopyridine 6-H); 7.61 (d,, 2H, phenyl C2-H and C6-H); 8.19-8.22(m, 3H, phenyl C3-H , C5-H and oxazolopyridine C7-H); 8.48 (d, 1H, oxazolopyridine C5-H); 12.[illegible] (s, IH, NH-N= D_2O exchangeable).
EIMS (m/z) for Vd: M/z (%): 368 $(M+2)^+$ (0.52), 366$(M)^+$ (10.68).

General procedure for 2-{4-[N²(Bis(cyano) methylene) hydrazino] phenyl) imidazo(or oxazolo) [4,5-*b*] pyridines VIa-d:

The respective diazonium salts (R= H,Br) solution was added drop-wise to a solution of malononitrile (0.66g. 0.01mol) in ethanol containing (1.5g, 0.011mol) of sodium acetate trihydrate with stirring and cooling. The reaction mixture was kept in ice for 2 h and then filtered. The product was dried and crystallized (Table 3).

Table3: 2-{4-[N²(Bis(cyano) methylene) hydrazino] phenyl} imidazo(or oxazolo) [4,5-*b*] pyridines VIa-d:

VI	X	R	m.p.(°C) solvent of cryst. yield	Mol. Form. (mol. wt.)	Analysis %	
					Calcd.	Found
a	NH	H	>300 DMF/MeOH 80	$C_{15}H_9N_7$ 287.28	C 62.71 H 3.16 N 34.13	62.55 3.30 34.50
b	NH	Br	>300 DMF/MeOH 83	$C_{15}H_8N_7Br$ 366.18	C 49.20 H 2.20 N 26.78	49.70 2.60 26.30
c	O	H	258-261 DMF 83	$C_{15}H_8N_6O$ 288.26	C 62.50 H 2.80 N 29.15	62.44 2.34 29.61
d	O	Br	270-274 DMF 85	$C_{15}H_7N_6BrO$ 367.16	C 49.07 H 1.92 N 22.88	48.95 1.69 22.90

(I.R: KBr cm^{-1}) Str.: forVIc :3650-3000 (NH), 2200 (CN, malonyl nitrile moiety), 1630-1590 (C=N in oxazolo and pyridine moieties)
^{1}H-NMR (DMSO , δ-ppm) forVIc:7.40 (t ,IH, pyridine C6-H); 7.88 (d,, 2H, phenyl C2-H and C6-H);8.22(m, 3H, phenyl C3-H and C5-H and oxazolopyridine C7-H); 8.54 (d, 1H, oxazolopyridine C5-H); 10.95 (s, IH, NH-N=C , D_2O exchangeable) .

EIMS (m/z) forVIc:M/z (%): 289 $(M+1)^{+\cdot}$ (18.4), 288$(M)^{+\cdot}$ (100).

General procedure for 2-{4-[N^2- (3,5-Diamino-pyrazol-4-ylidene) hydrazino] phenyl} imidazo (or oxazolo)[4,5-*b*]pyridines VIIa-d:

To a solution of the corresponding dicyano derivative VIa-d (0.01mol) in ethanol (20ml), hydrazine (0.5 g, 99%, 0.01mol) was added and refluxed for 0.5 h. The reaction mixture was evaporated, washed with water, dried and crystallized (Table 4).

Table 4: 2-{4-[N^2- (3,5-Diaminopyrazol-4-ylidene) hydrazino] phenyl} imidazo(or oxazolo)[4,5-*b*]pyridines VIIa-d:

VII	X	R	m.p.(°C) solvent of cryst. yield	Mol. Form. (Mol. wt)	Analysis %	
					Calcd.	Found
a	NH	H	>300 DMF 82	$C_{15}H_{13}N_9$ 319.33	C 56.42 H 4.10 N 39.48	56.77 3.75 39.50
b	NH	Br	>300 DMF 89	$C_{15}H_{12}N_9Br$ 398.22	C 45.24 H.3.04 N 31.66	45.70 2.60 31.30
c	O	H	258-261 DMF/ propanol 85	$C_{15}H_{12}N_8O$ 320.31	C 56.25 H 3.78 N 34.98	56.44 3.53 34.61
d	O	Br	270-274 DMF/ propanol 88	$C_{15}H_{11}N_8BrO$ 399.20	C 45.13 H 2.78 N 28.07	45.50 2.45 28.32

(I.R: KBr cm^{-1}) Str.: forVIIc : 3520-3000 (NH_2, NH), 1620 (C=N, oxazolo moiety), 1605 (C=N, pyridine moiety), 1570 (C=N, pyrazole moiety).

^{1}H-NMR (DMSO , δ-ppm) for VIIc:6.33(s, 4H, $2NH_2$, D_2O exchangeable); 7.44 (t ,1H, oxazolopyridine C6-H); 7.91 (d, 2H, phenyl C2-H and C6-H);8.25(m, 3H, oxazolopyridine C7-H ,phenyl C3-H and C5-H and); 8.54 (d, 1H, oxazolopyridine C5-H); 10.85 (s, IH, HN-N=C, D_2O exchangeable) .

EIMS (m/z) for VIIc: M/z (%): 321 $(M+1)^{+\cdot}$ (24.2), 320$(M)^{+\cdot}$ (100).

General procedure for 2-[4-Arylazophenyl] imidazo (or oxazolo)[4,5-*b*] pyridines VIIIa-k.

Diazonium salt II (0.01 mol, X =NH,O, R= H,Cl,Br,I) was added step-wise while cooling in ice/ salt mixture to a solution of the respective phenolic compound (0.01 mol) in an aqueous solution of sodium hydroxide (4 ml, 10%) with stirring and cooling. The reaction mixture was kept in ice for 2 h and then filtered, washed, dried and crystallized. (Table 5).

^{1}H-NMR (DMSO , δ-ppm) for VIIIa:

7.02 (d,2H,C3-H and C5-H of phenol moiety); 7.31 (t, 1H, C6-H of imidazopyridine); 7.87 (d, 2H, C2-H and C6-H of phenol moiety); 8.07(m,3H, C2-H , C6-H of phenyl and C7-H of imidazopyridine); 8.41(m,3H,C3-H , C5-H of phenyl and C5-H of imidazopyridine); 10.41 (s, IH, OH, D_2O exchangeable); 13.6(s,1H,NH of imidazopyridine, D_2O exchangeable).

EIMS (m/z) for VIIIa: M/z (%): 316 $(M+1)^{+\cdot}$ (28.39), 315$(M)^{+\cdot}$ (100).

EIMS (m/z) for VIIIc: M/z (%) 445$(M+2)^{+\cdot}$ (40.31),443$(M)^{+\cdot}$ (43.82),, 261 (100).

^{1}H-NMR (DMSO , δ-ppm) for compound VIIIf:

6.8 (d, 1H, C3-H of naphthol moiety); 7.25 (t, 1H, C6-H of imidazopyridine); 7.49 (t, 1H, C6-H of naphthol moiety) ; 7.64 (t, IH, C7-H of naphthol moiety); 7.70 (d, 1H, C8-H of naphthol moiety); 7.9 (d, C7-H of imidazopyridine and C5-H of naphthol moiety); 8.17 (d,1H, C6-H of phenyl); 8.4 (d, 2H, C5-H of phenyl and C4-H of naphthol moiety); 8.5 (d, 1H, C5-H of imidazopyridine); 8.8 (s, 1H, C2-H of phenyl); 13.66(br.s, 1H, imidazopyridine NH, D_2O exchangeable);15.74(S, 1H, OH, D_2O exchangeable)

EIMS (m/z) for VIIIf:
M/z (%): 493 $(M+2)^{+\cdot}$ (3.43),491$(M)^{+\cdot}$ (100).

^{1}H-NMR (DMSO , δ- ppm) forVIIIh:

2.21 (s,, 1H, CH_3); 6.98(d,1H, C5-H of *o*-cresol moiety); 7.45(t, 1H, C6-H of oxazolopyridine); 7.69 (d, 2H, C2-H and C6-H of *o*-cresol moiety); 8.02 (d, 2H, C2-H and C6-H of phenyl); 8.26(d, 1H, C7-H of oxazolopyridine); 8.41 (d, 2H, C3-H and C5-H of phenyl); 8.56(d, 1H, C5-H of oxazolopyridine); 10.39(s, IH, OH, D_2O exchangeable).

EIMS (m/z) for VIIIh: M/z (%): 331 $(M+1)^{+\cdot}$ (20.54), 330$(M)^{+\cdot}$ (100).

^{1}H-NMR (DMSO , δ- ppm) forVIIIj:

6,81 (d, 1H, C3-H of naphthol moiety); 7.4 (m, 2H, C6-H of naphthol moiety and C6-H of oxazolopyridine); 7.5-7.7 (m, 2H, C7-H and C8-H of naphthol moiety); 7.91-8.02 (m, 3H, C2-H, C6-H of phenyl and C5-H of naphthol moiety); 8.24 (d, 1H, C7-H of oxazolopyridine); 8.35 (d, 2H, C3-H and C5-H of phenyl); 8.53 (d, 1H, C4-H of naphthol moiety oxazolopyridine); 8.56 (d, 1H, C5-H of oxazolopyridine); 15.87 (S, 1H, OH, D_2O exchangeable)

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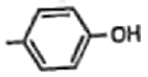
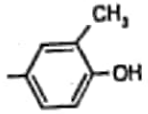
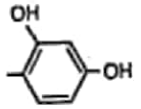
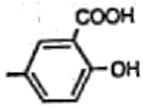
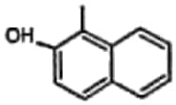
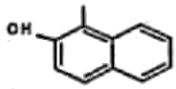
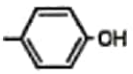
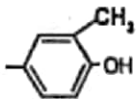
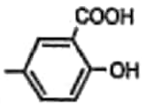
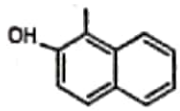
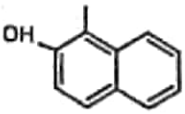
Table 5: 2-[4-Arylazophenyl] imidazo (or oxazolo)[4,5-*b*] pyridines VIIIa-k.

VIII	X	R	Ar	m.p.(°C) solvent of cryst. yield	Mol. Form. (mol. wt.)	Analysis % Calcd.	Found
a	NH	H		>300 DMF/EtOH 81	$C_{18}H_{13}N_5O$ 315.33	C 68.57 H 4.16 N 22.21	68.22 4.33 21.95
b	NH	H		>300 Acetic acid 80	$C_{19}H_{15}N_5O$ 329.36	C 69.30 H 4.59 N 21.26	68.80 4.30 21.62
c	NH	H		>300 DMF\ toluene 83	$C_{18}H_{13}N_5O_2$ 331.33	C 65.25 H 3.96 N 21.16	65.64 4.00 21.20
d	NH	H		>300 DMF\ toluene 77	$C_{19}H_{13}N_5O_3$ 359.34	C 63.51 H 3.65 N 19.49	63.52 3.15 19.40
e	NH	Br		>300 Acetic acid 75	$C_{22}H_{14}N_5OBr$ 444.29	C 59.47 H 3.17 N 15.76	59.80 2.97 15.75
f	NH	I		>300 Acetic acid 76	$C_{22}H_{14}N_5OI$ 491.29	C 53.78 H 2.88 N 14.26	53.80 3.30 14.36
g	O	H		>300 DMF\ toluene 80	$C_{18}H_{12}N_4O_2$ 316.32	C 68.35 H 3.83 N 17.71	68.55 4.02 17.34
h	O	H		290-293 DMF\ toluene 67	$C_{19}H_{14}N_4O_2$ 330.35	C 69.09 H 4.27 N 16.96	68.90 4.22 16.54
i	O	H		280-283 DMF\ toluene 66	$C_{19}H_{12}N_4O_4$ 360.33	C 63.33 H 3.37 N 15.54	63.33 3.32 15.50
j	O	H		>300 DMF\ toluene 60	$C_{22}H_{14}N_4O_2$ 366.38	C 72.12 H 3.86 N 15.29	71.97 3.54 15.71
k	O	Br		269-271 DMF\ toluene 82	$C_{22}H_{13}N_4O_2Br$ 445.27	C 59.34 H 2.94 N 12.58	59.80 3.20 12.75

(I.R: KBr γ cm $^{-1}$) Str. for VIIIa-k : all these compounds showed the following general absorption band: 3650- 3150 (OH & NH in imidazopyridines & COOH in VIII d , i), 1640-1620 (C=N of oxazolo or imidazo moiety), 1615-1600 (C=N of pyridine moiety),1580-1560 (N=N).

EIMS(m/z) for VI$_{+}$i:
M/z (%): 367(M+1)$^{\cdot}$ (25.32), 366(M)$^{\cdot+}$ (10

EIMS(m/z) for VIIIk: M/z (%): 446(M+2)$^{\cdot+}$ (50.54), 444(M)$^{\cdot+}$ (53.51), 143(100).

General procedure for 2-[4-Arylidenaminophenyl]imidazo (or oxazolo)[4,5-*b*]pyridines IXa-v

To a solution of the corresponding amine Ia-h (0.01 mol) in absolute ethanol (30 ml) containing 0.5ml of glacial acetic acid, the corresponding aromatic aldhyde (0.01mol) was added and heated under reflux for 3h. The reaction mixture was evaporated under vacuum. The residue left was washed, filtered, dried and crystallized (Table 6).

Table 6: 2-[4-Arylidenaminophenyl]imidazo (or oxazolo)[4,5-*b*]pyridines IXa-v

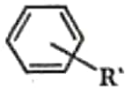
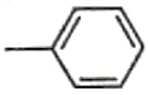
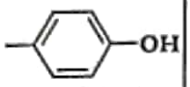
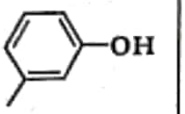
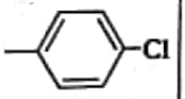
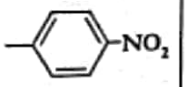
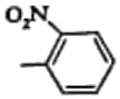
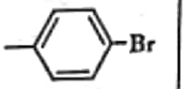
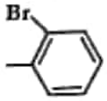
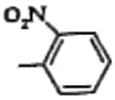
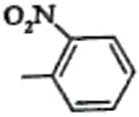
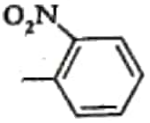
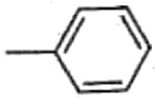
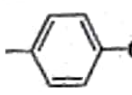
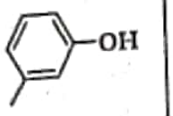
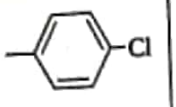
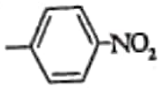
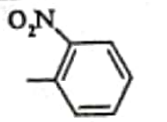
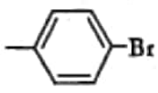
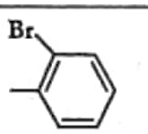
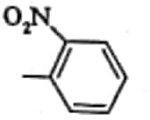
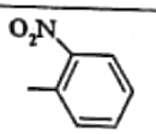
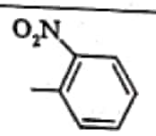
IX	X	R		m.p.(°C) solvent of cryst. yield	Mol. Form. (mol. wt)	Analysis %	
						Calcd.	Found
a	NH	H		>300 Dioxan/ethanol 76	$C_{19}H_{14}N_4$ 298.35	C 76.49 H 4.73 N 18.78	76.33 4.29 18.68
b	NH	H		>300 Dioxan/ethanol 71	$C_{19}H_{14}N_4O$ 314.35	C 72.60 H 4.50 N 17.82	72.60 4.36 17.63
c	NH	H		>300 Dioxan/ethanol 71	$C_{19}H_{14}N_4O$ 314.35	C 72.60 H 4.50 N 17.82	72.60 4.99 17.44
d	NH	H		>300 Acetic acid 69	$C_{19}H_{13}N_4Cl$ 332.80	C 68.57 H 3.94 N 16.84	68.88 4.10 16.51
e	NH	H		>300 DMF\ toluene 82	$C_{19}H_{13}N_5O_2$ 343.34	C 66.47 H 3.82 N 20.40	66.16 3.88 20.11
f	NH	H		>300 DMF\ toluene 68	$C_{19}H_{13}N_5O_2$ 343.34	C 66.47 H 3.82 N 20.40	66.70 4.02 20.30
g	NH	H		>300 Acetic acid 81	$C_{19}H_{13}N_4Br$ 377.24	C 60.49 H 3.47 N 14.85	60.20 3.83 14.80
h	NH	H		270-273 Dioxan/ethanol 79	$C_{19}H_{13}N_4Br$ 377.24	C 60.49 H 3.47 N 14.85	60.77 3.79 14.94
i	NH	Cl		>300 Acetic acid 76	$C_{19}H_{12}N_5O_2Cl$ 377.79	C 60.41 H 3.20 N 18.54	60.89 3.50 18.30
j	NH	Br		>300 Acetic acid 77	$C_{19}H_{12}N_5O_2Br$ 422.24	C 54.05 H 2.86 N 16.59	54.51 2.43 16.81
k	NH	I		>300 Acetic acid 79	$C_{19}H_{12}N_5O_2I$ 469.23	C 48.63 H 2.58 N 14.91	48.68 2.42 14.72
l	O	H		>300 Dioxan/propanol 69	$C_{19}H_{13}N_3O$ 299.33	C 76.24 H 4.38 N 14.04	76.25 4.35 14.10
m	O	H		235-238 Dioxan/propanol 69	$C_{19}H_{13}N_3O_2$ 315.33	C 72.37 H 4.16 N 13.33	72.00 4.33 13.02

Table 6 (Cont.)

n	O	H		233-235 Dioxan/propanol 72	$C_{19}H_{13}N_3O_2$ 315.33	C 72.37 H 4.16 N 13.33	72.44 4.01 13.11
o	O	H		258-261 Dioxan/propanol 74	$C_{19}H_{12}N_3ClO$ 333.77	C 68.37 H 3.62 N 12.59	68.40 3.20 12.30
p	O	H		>300 Acetic acid/ H_2O 73	$C_{19}H_{12}N_4O_3$ 344.33	C 66.28 H 3.50 N 16.27	66.58 3.34 16.00
q	O	H		280-283 Dioxan/propanol 69	$C_{19}H_{12}N_4O_3$ 344.30	C 66.28 H 3.50 N 16.27	66.52 3.11 16.02
r	O	H		260-262 Dioxan/propanol 66	$C_{19}H_{12}N_3OBr$ 378.23	C 60.34 H 3.20 N 11.11	60.73 2.97 10.85
s	O	H		256-259 Acetic acid/ H_2O 81	$C_{19}H_{12}N_3BrO$ 378.23	C 60.34 H 3.20 N 11.11	60.60 3.00 10.84
t	O	Cl		204-207 Dioxan/propanol 88	$C_{19}H_{11}N_4ClO_3$ 378.77	C 60.25 H 2.93 N 14.79	60.22 3.20 14.34
u	O	Br		269-273 Acetic acid/ H_2O 68	$C_{19}H_{11}N_4BrO_3$ 423.23	C 53.92 H 2.62 N 13.24	53.80 3.11 12.75
v	O	I		250-253 Acetic acid/H_2O 69	$C_{19}H_{11}N_4I\ O_3$ 470.22	C 48.53 H 2.36 N 11.91	48.68 2.42 11.72

(I.R :KBr cm $^{-1}$)str: Compounds IXa-v showed the following general absorption bands:
3600-3200- (NH in imidazopyridines and OH in compounds IXb,c,m,n),1640-1620 (C=N of oxazolo or imidazo moiety), 1620-1600 (C=N of pyridine moiety),1480- 1500(C=N of azomethine).

^{1}H-NMR (DMSO,δ-ppm) for IXa

7.29(t, IH, C6-H of oxazolopyridine); 7.41-7.70 (m,5H,of benzylidine); 7.84-8.09(d, 3H, C2-H and C6-H of phenyl and C-7H of oxazolopyridine); 8.20-842(d,3H,C3-H and C5-H of phenyl and C5-H of oxazolopyridine); 8.73(s,1H,CH of azomethine); 13.50 (s, IH, imidazopyridine NH, D_2O exchangeable).

EIMS (m/z): forIXa:

m/z (%): 299(M+1)$^+$ (20.41), 298 (M)$^+$ (100).

EIMS (m/z): forIXc:

m/z (%): 315(M+1)$^+$ (20.61), 314 (M)$^+$ (100).

EIMS (m/z): forIXg:

m/z (%): 378(M+2)$^+$ (100), 376 (M)$^+$ (97.53)

^{1}H-NMR (DMSO,δ-ppm forIXn:

7.31 (t, 1H, C-6H of oxazolopyridine);7.34-7.49(m, 6H, C-2H,C-4-H, C-5H, C6-H of C_6H_4-OH and C2-H,C6-Hof phenyl); 8.19-8.25(t,3H ,C3-H,C5-H of phenyl, C7-H of oxazolopyridine); 8.52 (d, 1H, C5-H of oxazolopyridine); 8.60(s,1H, azomethine CH) 9.61(s, 1H, OH, D_2O exchangeable).

EIMS (m/z): forIXn:

m/z (%): 316(M+1)$^+$ (21.91), 315 (M)$^+$ (100).

EIMS(m/z) : forIXp:

m/z (%): 345(M+1)$^+$ (22.48), 344 (M)$^+$ (100).

General procedure for 2-[4-(3-Chloro-2-oxo -4-substituted phenylazetidin-1-yl) phenyl]imidazo(or oxazolo)[4,5-*b*]pyridines Xa-d

To a well-stirred solution of the respective azomethine IX d,g,o or r (0.01mol)and triethyl amine (.02 mol)in dry dioxan (50 ml), monochloroacetyl-chloride(2.25 g,0.02 mol) was added drop-wise at room temperature. The reaction mixture was stirred for another 5h and left at room temperature for 5 days. The precipitated triethylamine hydrochloride was filtered off; the filtrate was concentrated to a minimum volume and poured into cold water. The solid product was separated, dried and crystallized from the appropriate solvent (Table 7).

Table (7): 2- [4- (3- Chloro-2-oxo -4- substituted phenylazetidin-1-yl) phenyl]imidazo (or oxazolo) [4,5-*b*] pyridines Xa-d

X	X	R	m.p.(°C) solvent of cryst. yield	Mol. Form. (mol. Wt.)	Analysis %	
					Calcd.	Found
a	NH	Cl	255-259 EtOH/Dioxan 63	$C_{21}H_{14}N_4Cl_2O$ 409.27	C 61.63 H 3.45 N 13.69	61.63 3.77 13.28
b	NH	Br	288-291 EtOH/ Dioxan. 68	$C_{21}H_{14}N_4BrClO$ 453.72	C 55.59 H 3.11 N 12.35	55.79 3.25 12.65
c	O	Cl	218-221 Dioxan 63	$C_{21}H_{13}N_3Cl_2O_2$ 410	C 56.59 H 2.94 N 9.43	9.80
d	O	Br	228-231 Dioxan 68	$C_{21}H_{13}N_3BrClO_2$ 454.5	C 53.20 H 2.76 N 8.86	8.53

(I.R :KBr cm $^{-1}$)str. for compound Xb :

3650-3200 (NH), 1720 (C=O), 1630 (C=N of imidazo moiety), 1610 (C=N pyridine), 780 (C-Cl).

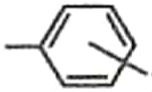
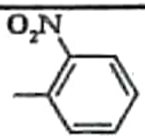
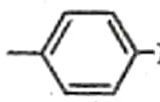
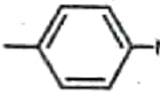
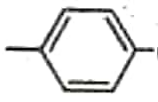
^{1}H-NMR (DMSO,δ-ppm) for Xb:

7.21 (t , 1H , C6-H of imidazopyridine); 7.68-8.2(m, 7H, C2-H, C3-H, C5-H,C6-H of C_6H_4-Br,C2-H,C6-H of phenyl and C-7 of imidazopyridine); 8.31 (d,2H,C3-H and C5-H of phenyl); 8.34(d, IH, imidazopyridine C5-H); 8.6 (d,1H,N=CH-of β-lactam ring); 9.93 (d,1H,COCHCl of β-lactam ring, D_2O exchangeable); 12.7 (s,1H,NH, imidazopyridine NH, D_2O exchangeable).

General procedure for 2-[4-(4-Oxo-2-subsituted phenylthiazolidin-3-yl) phenyl] imidazo (or oxazolo) [4,5-*b*]pyridines XIa-d

A mixture of equimolar amounts of the appropriate azomethine derivatives IX f,g,o or p and mercaptoacetic acid (0.01 mol of each) in dry benzene(100 ml) was refluxed using a water separator until theoretical amount of water had been collected. Benzene was evaporated under reduced pressure and the residue was crystallized from the appropriate solvent (Table 8).

Table 8: 2-[4-(4-Oxo-2-subsituted phenylthiazolidin-3-yl) phenyl] imidazo (or oxazolo) [4,5-*b*]pyridines XIa-d

XI	X		m.p.(°C) Solv.of cryst. yield	Mol. Form. (mol. wt.)	Analysis %	
					Calcd.	Found
a	NH		255-259 Acetic acid 69	$C_{21}H_{15}N_5O_3S$ 417.43	C 60.34 H 3.62 N 16.78	60.56 3.92 16.58
b	NH		288-291 Dioxan /EtOH. 68	$C_{21}H_{15}N_4BrOS$ 451.33	C 55.89 H 3.35 N 12.41	55.41 3.69 12.00
c	O		218-221 Dioxa n/ EtOH 65	$C_{21}H_{14}N_4O_4S$ 418.40	C 60.28 H 3.37 N 13.39	59.91 3.47 13.44
d	O		228-231 Dioxin/ EtOH 62	$C_{21}H_{14}N_3ClO_2S$ 407.54	C 61.89 H 3.43 N 10.32	61.88 2.90 10.61

(I.R :KBr cm $^{-1}$)str.for **XIc:** showed the following absorption bands:

1720(C=O), 1620 (C=N of oxazolo moiety), 1600 (C=N of pyridine moiety).

^{1}HNMR (DMSO,δ-ppm) for compound (XIc)

3.95-4.16 (d of d ,2H, CH_2 of oxothiazolidinyl group);6.87(s,1H,-N-CH-S-); 7.39 (t, IH, C6-H of oxazolopyridine); 7.61-7.75 (m,4H,C2-H,C6-H of C_6H_4-NO_2,C2-H and C6-H of phenyl group);8.16 (d, 5H, C3-H , C5-H of C_6H_4-NO_2 ,C-3, C5-H of phenyl group and C7-H of oxazolopyridine); 8.50 (d,1H,C5-H of oxazolopyridine).

EIMS(m/z)for(IVc):

m/z (%):420 $(M+2)^+$ (5.2 %), 418 $(M)^+$ (100).

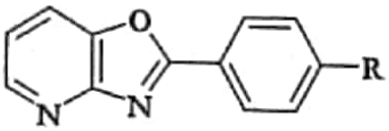
Molecular modeling general methodology:

All molecular modeling studies were performed on a Silicon Graphics workstation, running under IRIX64 operating system, using Hip Hop procedure of catalyst software (version 7.7).[29] The molecular model produced by catalyst is called a hypothesis (hypothetical model). A catalyst hypothesis can contain an arbitrary set of 3D data, 2D (topology) data, 1D (scaler) parameters, and constraint descriptions. The basic modeling methodologies leading to the pharmacophore- based alignments (e.g., conformational analysis, molecule fitting, etc.), were performed with catalyst using the implemented chemical features [30] and the energy minimization procedure. Conformational analysis was an implemented in the program using the above described minimizer coupled to "poling" function to assess conformational variation and the BEST algorithm. The latter intends to optimize the conformational coverage versus the size assembly[31].

Catalyst pharmacophore construction (hypothesis generation):

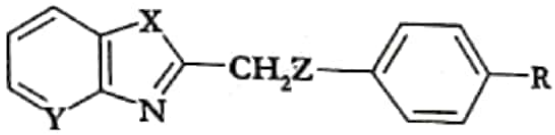
Generally, the hypothesis generation within catalyst was based on the analysis of the training (lead) compounds in their most stable conformation. Consequently, the common chemical features of the training set compounds as well as the valid geometric arrangement of these chemical features are used to generate the pharacophore model.

In the present study, best conformational analysis, using catalyst program, was performed using 7 lead compounds **(12a-c)** and **(13a-d)**[1] order to approximate all energetically accessible shapes the molecule may adopted.



(12a-c)

R = $(CH_3)_3$C,Cl,Br



(13a-d)

X = NH,O,S **Y= N, CH**

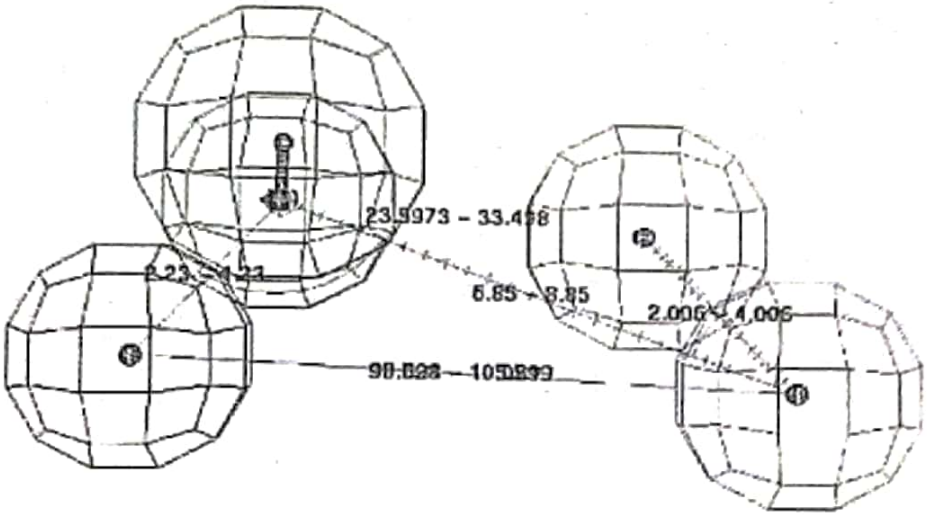
Z= O, S, CH_2 **R = H,Cl,Br**

Best conformational analysis was performed for each compound using a threshold of 250 conformers per molecule and a maximum value of 20 Kcal/mol for conformer energy.

Afterwards, the emerged conformers for each lead compound were used to build up the hypothetical model using Hip Hop method of catalyst program. Hip Hop tool identifies the common chemical features within the lead compounds starting from the conformers of the principle compound in the lead compounds. Compound 10(Y = CH, X = S, Z = O, R = Cl) took a value of two in the principle column and considered to be the principle one. In addition, the following parameters were loaded into the catalyst program in order to specify the hypothesis where, MaxOmitFeat sited to be one for all compounds. Moreover, Hydrogen bond acceptor (HBA), Hydrogen bond donor (HBD) and Hydrophobic (H) functions were specified to be the chemical features that would be considered in the generation of the hypothetical model. At the end of these procedures, Catalyst program generate 7 hypotheses, ranked according to their scores, which most likely express the common chemical features of the lead compounds. Among the generated 7 hypothesis, the highest ranking one is the most likely expressed the common features composition of the lead compounds (Figure 1).

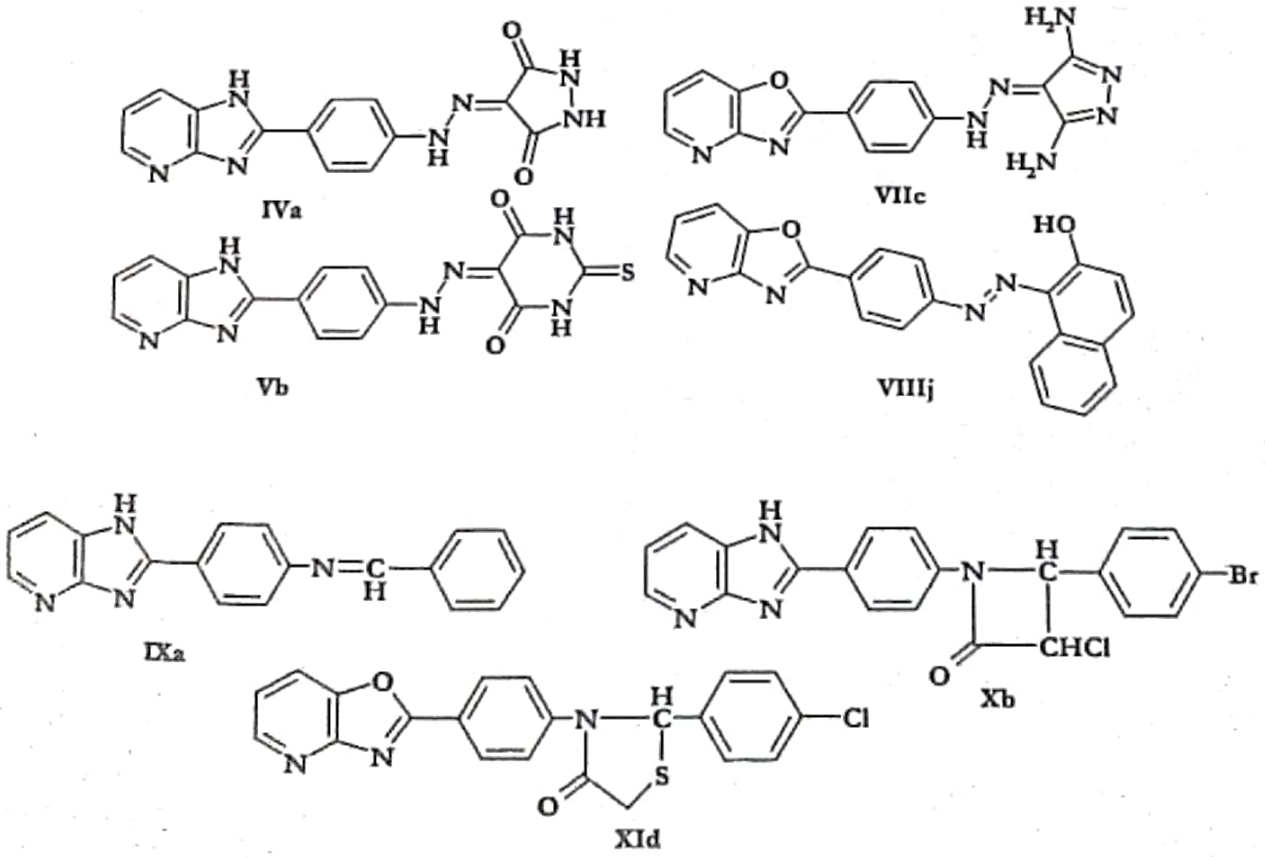
The highest ranking hypothesis composed of (4) four features (Two hydrophobic and two hydrogen bond acceptor). In order to test the generated pharmacophore model, the highest ranking hypothetical model was subjected for mapping with the principle compound 10(Y = CH, X = S,Z = O,R = Cl) and gave a fit value = 4 .

Fig 1:



Hypothesis with constraint dimension

Validation of the hypothetical model The performance of the modified hypothetical model was evaluated by fitting the following test compounds (IVa, Vb, VIIc , VIIIj, IXa, Xb and XId)

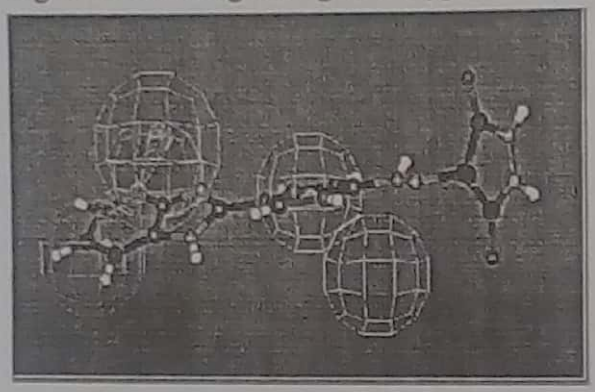


Fitting operations to the modified hypothetical model were accomplished through; firstly, best conformational analysis was done utilizing a threshold of 250conformers per molecule and a maximum value of 20 Kcal/mol for conformer energy. Secondly, the conformers of each compound in the test set were allowed to fit to the modified hypothesis using best fit option and the fit values of the test compounds were obtained. Table (9),Figure (2) the obtained fit value for each compound is a measure of how many and how well its functional features fit to the features of the pharmacophore.

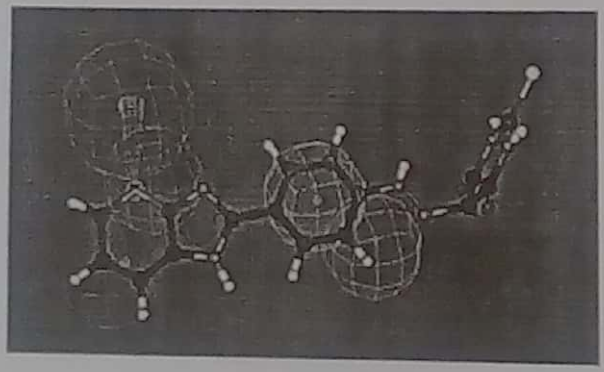
Table (9): Fit values of the test compounds

compound	Number of conformers	Fit value
IVa	90	2.60
Vb	42	2.59
VIIc	92	2.94
VIIIj	90	2.59
IXa	42	2.60
Xb	90	2.59
XId	92	2.94

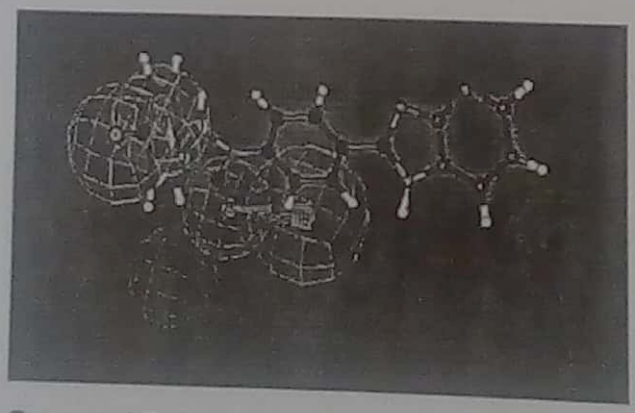
Figure 2: showing fitting with hypothesis



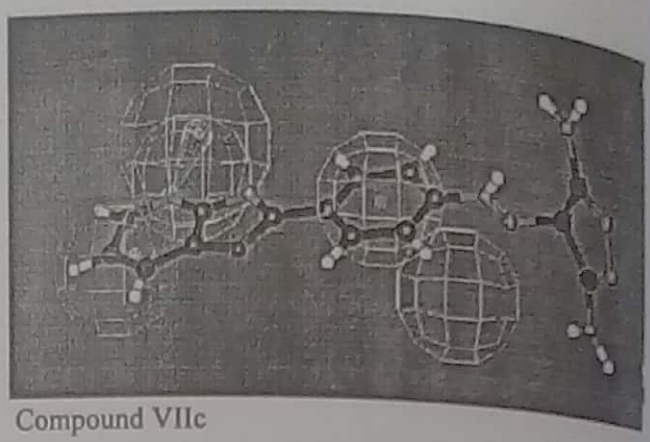
Compound IVa



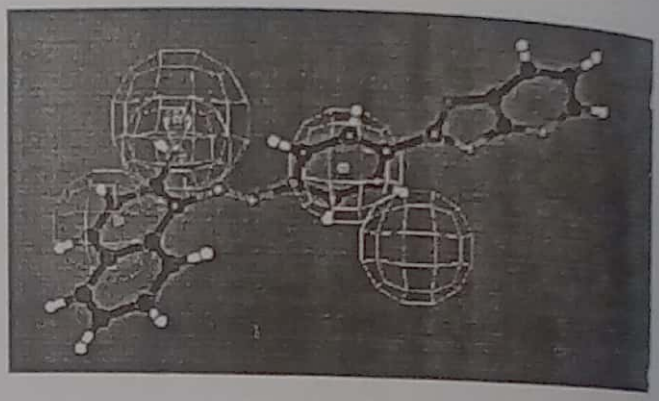
Compound Vb



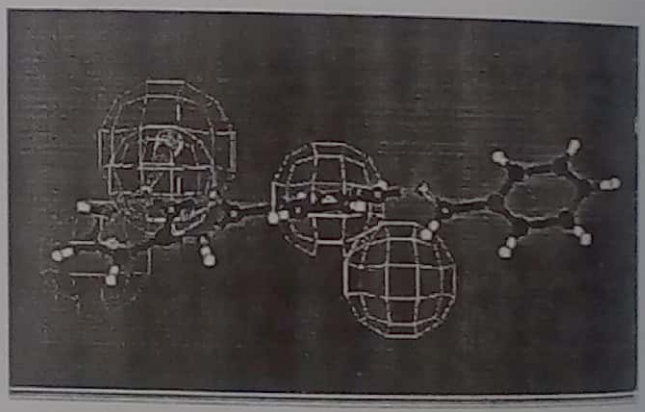
Compound IXa



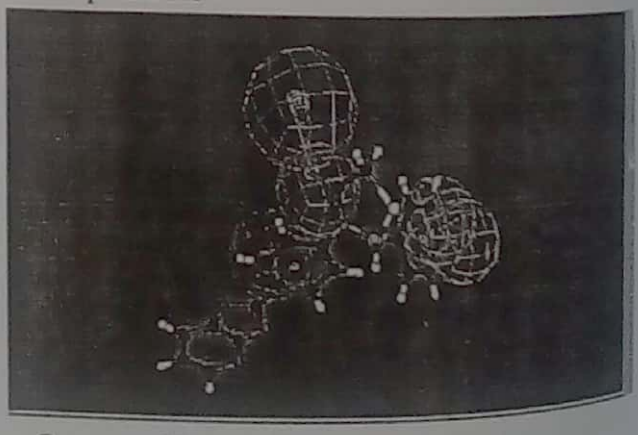
Compound VIIc



Compound VIIIj



Compound Xb



Compound XId

Preliminary antimicrobial screening[32]:

The antimicrobial activity of four compounds was tested against representatives of acid fast bacilli (*Mycobactrium Phelî*), Gram-positive bacteria (*Bacillus Subtilis, Sarcina Lutea and Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli, Proteus vulgaris and Pseudomonas aeruginosa*) and Yeast (*Candida albicans, Toruiopsis glabrata and Candida tropicalis*). Applying the agar diffusion disc method using trypticase soy agar medium (Difco) the

tested compounds were dissolved in DMSO at concentration of 20mg/5ml then 20µl were aseptically added to the discs of Whatmann No. 1filter paper 5mm diameter (400 µg/disc). 20µl of DMSO is used as negative control as well as discs of Ofloxacine (OFX, Oxoid) and Ammphotricine B,(AmpB,Oxoid),5 µg/disc each were used as a positive control.The discs were then placed onto the surface of the inoculated plates previously prepared. The plates were incubated inverted at 37°C for 24 h in case of bacteria and at 25°C for 48hr in case of fungi (yeasts). After incubation, the inhibition zones were recorded in mm and the results are interpreted as in table 10. Diameter less than 5mm indicates no effect.

RESULTS AND DISCUSSIONS

Most of the tested compounds showed moderate antimicrobial activity against Gram-negative bacteria *(Proteus vulgaris and Pseudomonas aeruginosa)*, but week or no effect against Gram-positive ones. However most of these compounds exhibited week or no antifungal as well as no effect against Mycobacterial species.

Table (10): Antimicrobial activity of tested compounds

Microorganisms	IVa	Vb	VIIc	VIIIj	IXa	Xb	XId	OFX	AM-PB
E.coli ATCC 10536	-	-	-	-	10	12	13	29	
Proteus vulgaris NCTC 4175	-	19	13	-	12	11	11	38	
Pseudomonas aeruginosa CNCMA 21	16	13	19	16	15	25	8	29	
Staphylococcus aureus ATCC 4175	-	-	-	-	-	18	8	32	
*Sarcina lutea**	10	-	8	10	10	18	5	30	
Bacillus subtilis NCTC 6633	10	10	-	-	18	20	-	36	
*Mycobacterium pheli**	-	-	-	-	-	5	-	25	
Candida albicans ATCC 60198	8	-	-	8	-	12	10		25
*Candida tropicalis**	-	-	-	-	-	-	-		22
*Toruloposis glabrata**	8	-	-	8	-	-	-		24

*: OFX: ofloxacine (5 µg/disc) and AMP.B: (5 µg/disc) positive control.
++: diameter of 11-15, +++diameter of 16-22mm, ++++ diameter more than 23mm. -no inhibition zone, + diameter of inhibition zone 10mm, *: laboratory collection strains.

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تصميم و تشييد والنمذجة الجزيئية لبعض مشتقات الاميدازو والأوكسازولوبيردين ذات الفعالية البيولوجية

*ايمان كمال أحمد عبد العال ، أسامة متولي البدرى ، سميحة محمد علي رشدي ومرفت مصطفى الضانى

قسم الكيمياء العضوية – كلية الصيدلة – جامعة القاهرة – القاهرة

* قسم الكيمياء العضوية – كلية الصيدلة – جامعة بني سويف – بني سويف – مصر

يتضمن البحث تحضير بعض أملاح الديازونيوم وتفاعلها مع استر حمض المالونيك والمالونونيتريل لتعطي مركبات وسيطة . وبتفاعل هذه المركبات مع اثنين من الهيدرازين واليوريا والثيويوريا أمكن الحصول على مركبات نهائية جديدة وفى النهاية يشمل البحث تحضير عدد من صبغات الأزو. كما يتضمن البحث تفاعل مركبات الأمين In-h ايضا مع عدد من الألدهيدات لتحضير مشتقات الآزوميثين والتي بدورها تم تفعيل بعضها مع كلورو كلوريد الاستيل وحمض الثيوجليكوليك لتعطي مركبات حلقيه جديدة .

كما يشمل البحث اختبار بعض من المركبات المشيدة كمضادات للميكروبات ودراسة درجة تأثير هذه المركبات على المستقبلات الخاصة بها وذلك من خلال استخدام بعض برامج الحاسب الآلي.