



## Solving Bi-harmonic Cauchy problem using a meshless collocation method

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### Abstract

In this article a fourth order differential boundary value problem is solved using a mesh less collocation method. The efficiency of the proposed methods is illustrated by solving problems with some examples of a polynomial and Non polynomial exact solutions and by using Conjugate gradient method and Conjugate gradient Least square algorithms and the numerical stability is verified by using a noise for the input boundary data.

**Keywords:** Bi-Laplacian differential equation, Inverse Cauchy problem, mesh less method. Conjugate Gradient Method, Conjugate Gradient Least Square.

### حل مسألة كوشي ثنائية التوافق باستخدام طريقة التجميع بدون شبكة

بيداء خليل مصطفى, دعاء جاسم, عذراء فالح حسن, ابتهاج ثابت, فاطمة محمد عبود

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### الخلاصة

في هذا البحث تم حل مشكلة القيمة الحدية التفاضلية من الدرجة الرابعة باستخدام طريقة التجميع غير الشبكية. تم التأكد من كفاءة الطريقة المقترحة من خلال حل مشكلات لبعض الأمثلة مع حلول مضبوطة من نوع متعددات الحدود وغير متعددات الحدود وباستخدام خوارزميات طريقة التدرج المترافق و طريقة التدرج المترافق للتربيعات الصغرى كما تم التحقق من الاستقرار العددي باستخدام ضوضاء لبيانات الحدود.

**الكلمات المفتاحية :** المعادلات التفاضلية ثنائية لابلاس, مسألة كوشي العكسية, طريقة لا شبكية, طريقة التدرج المترافق, طريقة التدرج المترافق للتربيعات الصغرى



## Introduction

The fourth order differential equation has many applications in physics (in the fields of fluid and solid mechanics), mathematics, engineering mathematics and computing sciences. In the last decades several iterative and non-iterative methods have been developed where the Dirichlet and or Dirichlet and Neumann conditions are satisfied on the boundary. Some authors have treated the fourth order problem directly and solved the problems in its original form, other authors are preferred to split the problem in two problems of second order, i.e. a couple of problems with Laplace equation, this permit them to benefit from the advantage of the second order equation and all the results lied to them. Recently, a new iterative method has been proposed based on the transformation of the bi-harmonic equation with the Dirichlet and Neumann boundary conditions to an optimization problem similar to an optimal control one [Boujaj et al, ].Some authors proposed some numerical techniques based on finite difference method (FDM) (see [Boujaj et al, ].Some authors proposed some numerical techniques based on finite difference method (FDM) (see [Aboud F.,Nachaoui&Nachaoui M.(2021) , Andrieux, G., Rondi,L., L.,Rossent, E. &Vessella,S. (2009) , Andrieux, S. Baranger, T.N .&Ben Abda, A.(2006) ] by splitting the biharmonic problem into two decoupled Poisson equations). Some other works based on the finite element method (FEM) [Andrieux,S.Baranger, T.N.& Ben Abda, (2006).], or on a mixed finite volume method (see [Belgacem,F.B.(2007) ,Berdawood,K.A., Nachaoui, A., Saeed, R., Nachaoui, M. &Aboud, F. (2020), Berdawood,K.A., Nachaoui, A., Saeed, R., Nachaoui, M. &Aboud, F. (2021), Berdawood ,K.A., Nachaoui, A., Saeed, R., Nachaoui, M. &Aboud, F. (2021) ,Bergam,A., Chakib, A.,&Nachaoui,M.(2019) , Berntsson, F.,Kozlov, V.,A., Mpinganzima, L.&Turesson, B.O.(2017), Burger, M.(2001) , Cimetiere,A., Delvare, F. ,Jaoua, M.&Pons,F.(2001) , Chakib, A., Nachaoui,A.,Nachaoui, M.&ouaissa, H.(2018) , Chang .J.R., Yeih, W.&Shieh, M.H.(2001), Chen,J.T.& Chen, K.H.(1998) , Chi,C.C., Yeih, W.&Liu, C.S.(2009) , Choulli, M.(2009) ] and the references cited therein). A mesh lessMultiquadric (MQ) collocation method to solve bi-harmonic problems with discontinuous boundary conditions has been proposed in [Chantasiniwan S. Transf (2007)]. An iterative method based on the fixed point theory to solve biharmonic-type equation with mixed boundary conditions see [Dang QA. Mixe.Vietnam J



Math (1998), Dang QA.J APPL Math (2006), Dang QA.Thien NV. J APPL Math (2012)].Qingqu and Lizhen [Zhuang, Chen L, Legendre\_Galerkin.Comput Math APPL (2017)] have proposed ameshlesspectral element method based on the Legendre-Galerkin approximation to solve the two-dimensional bi-harmonic equation.

In this work, we propose a meshless collection method following the same method proposed by [Rashid et al., 2021]. For this we present the solution as a polynomial expansion and by verifying the Bi-Laplacian differential equation and the boundary condition with the given Cauchy data, we obtain a linear system, we solve this linear system by using CGM and CGLS algorithms by applying the proposed method for some examples with polynomial and non-polynomial exact solutions and we verify the stability of the numerical results by applying some noise on the given data.

The plan for the rest of this article is as follows, In section 2, the Inverse Cauchy problem bi-harmonic equation is stated. A numerical method based on the approximation of the solution by a polynomial expansion is proposed in section 3. The application of the proposed method on some examples with the numerical results in section 4. The stability of the numerical method is checked in section 5. In section 6 we give our conclusion.

## 2 inverse Cauchy problem bi-harmonic equation

We consider the inverse Cauchy problem of bi harmonic equation defined on an annular domain  $\Omega \setminus D_\beta \subset R^2$  with

$$\Omega = \{(r, \theta) : 0 \leq r < 1, \quad 0 \leq \theta \leq 2\pi\}$$

$$D_\beta = \{(r, \theta) : 0 \leq r < \beta, \quad 0 < \beta < 1, \quad 0 \leq \theta \leq 2\pi\}$$

With the boundary  $\Gamma_1 \cup \Gamma_2$

$$\Gamma_1 = \{(r, \theta) : r = \rho_e(\theta) \quad 0 \leq \theta \leq 2\pi\}$$

$$\Gamma_2 = \{(r, \theta) : r = \rho_i(\theta) \quad 0 \leq \theta \leq 2\pi\}$$



Where  $0 < \rho_e(\theta) \leq 1$  and  $0 < \rho_i(\theta) < 1$ . The problem is given as follows:

$$\Delta^2 u = F(x, y) \text{ in } \Omega \quad (1)$$

$$u(\rho, \theta) = u_0(\theta), \text{ on } \Gamma_1 \quad (2)$$

$$\partial_n u(\rho, \theta) = h_0(\theta), \text{ on } \Gamma_1 \quad (3)$$

$$\Delta u(\rho, \theta) = w_0, \text{ on } \Gamma_1 \quad (4)$$

$$\partial_n \Delta u(\rho, \theta) = w'_0, \text{ on } \Gamma_1 \quad (5)$$

The Cauchy data  $u, \partial_n u, \Delta u, \partial_n \Delta u$  are given on  $\Gamma_1$  which is called as the accessible part of the boundary, this part of the boundary is over determined (in which there are four boundary conditions), but unfortunately there is no data on  $\Gamma_2$  (no boundary condition in this part) so this part is known as under-determined or inaccessible part of the boundary. For these reason an inverse Cauchy problem for the bi-Laplacian is formulated to determine the unknown function  $u$  on the interior under-determined boundary  $\Gamma_2$ .

We recall that  $\partial_n$  is the outer normal derivative which is given by Rasheed et. al. 2021.

$$\partial_n u(\rho, \theta) = \eta(\theta) \left[ \frac{\partial u(\rho, \theta)}{\partial \theta} - \frac{\rho'}{\rho^2} \frac{\partial u(\rho, \theta)}{\partial \rho} \right] \quad (6)$$

$$\text{with } \eta(\theta) = \frac{\rho(\theta)}{\sqrt{\rho^2(\theta) + [\rho'(\theta)]^2}} \quad (7)$$

In general cases the radius  $\rho$  can be taken as a function  $\rho, \theta$  i.e. it is a variable, so we can calculate its derivative.

In this paper, we take a special case in which  $\rho$  is a constant, so  $\rho', \theta = 0$ .

In fact, the normal derivatives is given by the inner product of the gradient with the normal vector, i.e.  $\frac{\partial u}{\partial n} = \nabla u \cdot \vec{n}$ , so we can express the normal derivative in terms of the derivative with



respect to  $x$  and  $y$ . We take the polar coordinates, here the points  $(x, y)$  are the points with respect to the  $\rho, \theta$ .

$$\begin{aligned} \partial_n u(\rho, \theta) = & \eta(\theta) \left[ \cos(\theta) - \frac{\rho'}{\rho^2} \sin(\theta) \right] \partial_x(\Delta u) + \eta(\theta) \left[ \sin(\theta) \right. \\ & \left. - \frac{\rho'}{\rho^2} \cos(\theta) \right] \partial_y(\Delta u) \end{aligned} \quad (8)$$

## Expression of Solution as a polynomial expansion

We consider that the solution  $u(x, y)$  is expressed as the following polynomial expansion:

$$u(x, y) = \sum_{i=1}^m \sum_{j=1}^i c_{ij} x^{i-j} y^{j-1} \quad (9)$$

Now, we express the problem in (1-5) in form of the expansion in (9). To do so, we find

$$\partial_x u(x, y) = \sum_{i=1}^m \sum_{j=1}^i c_{ij} (i-j) x^{i-j-1} y^{j-1} \quad (10)$$

$$\partial_y u(x, y) = \sum_{i=1}^m \sum_{j=1}^i c_{ij} (j-1) x^{i-j} y^{j-2} \quad (11)$$

From which the different degree of derivatives are calculated to find  $\Delta u, \partial_n \Delta, \Delta^2 u$ .

$$\Delta u(x, y) = \sum_{i=1}^m \sum_{j=1}^i c_{ij} [(i-j)(i-j-1)x^{i-j-2}y^{j-1} + (j-1)(j-2)x^{i-j}y^{j-3}] \quad (12)$$

Then

$$\begin{aligned} \partial_x(\Delta u) = & \sum_{i=1}^m \sum_{j=1}^i c_{ij} [(i-j)(i-j-1)(i-j-2)x^{i-j-3}y^{j-1} \\ & + (i-j)(j-1)(j-2)x^{i-j-1}y^{j-3}] \end{aligned} \quad (13)$$



$$\partial_y(\Delta u) = \sum_{i=1}^m \sum_{j=1}^i c_{ij} [(i-j)(i-j-1)(j-1)x^{i-j-2}y^{j-2} + (j-1)(j-2)(j-3)x^{i-j}y^{j-4}] \quad (14)$$

By using (8), the normal derivative of the Laplacian is given by the following:

$$\begin{aligned} \partial_n(\Delta u)(x, y) = & \sum_{i=1}^m \sum_{j=1}^i c_{ij} \eta(\theta) [\cos(\theta) \\ & - \frac{\bar{\rho}}{\rho^2} \sin(\theta)] [(i-j)(i-j-1)(i-j-2)x^{i-j-3}y^{j-1} \\ & + (j-1)(j-2)(i-j)x^{i-j}y^{j-3}] + \eta(\theta) [\sin(\theta) \\ & - \frac{\bar{\rho}}{\rho^2} \cos(\theta)] [(i-j)(i-j-1)(j-1)x^{i-j-2}y^{j-2} \\ & + (j-1)(j-2)(j-3)x^{i-j}y^{j-4}] \end{aligned} \quad (15)$$

and

$$\begin{aligned} \Delta^2(x, y) = & \sum_{i=1}^m \sum_{j=1}^i c_{ij} (i-j)(i-j-1)(i-j-2)(i-j-3)x^{(i-j-4)}y^{(j-1)} \\ & + 2(i-j)(i-j-1)(j-1)(j-2)x^{(i-j-2)}y^{(j-3)} \\ & + (j-1)(j-2)(j-3)(j-4)x^{(i-j)}y^{(j-5)} \end{aligned} \quad (16)$$

The coefficients  $c_{ij}$  must be determined, the number of these coefficients  $c_{ij}$  is  $\frac{m(m+1)}{2}$ . To obtain a linear system we express  $c_{ij}$  as a vector  $\mathbf{c}$  of length  $n$  where the index  $ij$  is used to obtain the index of the components of  $\mathbf{c} = [\mathbf{c}_i]_{n \times 1}$  by taking  $i = \frac{i(i-1)}{2} + j$ , so the unknowns function  $u(x, y)$  can be expressed as an inner product of a row of variables, say  $\mathbf{v}'$ , with a column of coefficient vector  $\mathbf{c}$ , i.e.

$$u = \mathbf{v}' \cdot \mathbf{c} \quad (17)$$

where

$$\mathbf{v}' = [1, x, y, x^2, xy, y^2, x^3, \dots], \quad \mathbf{c} = \begin{bmatrix} c_1 \\ c_2 \\ c_3 \\ \vdots \\ c_n \end{bmatrix}$$



Similarly, the normal derivative  $\partial_n u$  can be represented as a scalar product of a row of variables, say  $\mathbf{e}$ , with a column of coefficient vector  $\mathbf{c}$ , i.e.  $u = \mathbf{e} \cdot \mathbf{c}$  where the component of  $\mathbf{e}$  are given by

$$e_k = \eta(\theta) \left[ (i-j)x^{i-j-1}y^{j-1} \left( \cos(\theta) - \frac{\bar{\rho}}{\rho^2} \sin(\theta) + (j-1)x^{i-j}y^{j-2} \left( \sin(\theta) - \frac{\bar{\rho}}{\rho^2} \cos(\theta) \right) \right) \right]. \quad (18)$$

Also, the Laplacian can be expressed as an inner product of a row of variables, say  $\mathbf{d}$ , with a column of coefficient vector  $\mathbf{c}$ , i.e.  $\Delta u = \mathbf{d} \cdot \mathbf{c}$  where the component of  $\mathbf{d}$  are given by

$$d_k = [(i-j)(i-j-1)x^{i-j-2}y^{j-1} + (j-1)(j-2)x^{i-j}y^{j-3}] \quad (19)$$

and the normal derivative of the Laplacian can be expressed as an inner product of a row of variables, say  $\mathbf{q}$ , with a column of coefficient vector  $\mathbf{c}$ , i.e.  $\partial_n \Delta u = \mathbf{q} \cdot \mathbf{c}$  where the component of  $\mathbf{q}$  are given by

$$\begin{aligned} e_k = \eta(\theta) & \left[ \cos(\theta) - \frac{\bar{\rho}}{\rho^2} \sin(\theta) \right] [(i-j)(i-j-1)(i-j-2)x^{i-j-3}y^{j-1} \\ & + (j-1)(j-2)(i-j)x^{i-j-1}y^{j-3}] \\ & + \eta(\theta) \left[ \sin(\theta) - \frac{\bar{\rho}}{\rho^2} \cos(\theta) \right] [(i-j)(i-j-1)(j-1)x^{i-j-2}y^{j-2} \\ & + (j-1)(j-2)(j-3)x^{i-j}y^{j-4}] \end{aligned} \quad (20)$$

Finally, the bi-Laplacian can be expressed as an inner product of a row of variables, say  $\xi$ , with a column of coefficient vector  $\mathbf{c}$ , i.e.  $\Delta^2 u = \xi \cdot \mathbf{c}$  where the component of  $\mathbf{q}$  are given by

$$\begin{aligned} \xi_k = & (j-1)(i-j-1)(i-j-2)(i-j-3)x^{i-j-4}y^{j-1} \\ & + 2(i-j)(i-j-1)(j-1)(j-2)x^{i-j-2}y^{j-3} \\ & + (j-1)(j-2)(j-3)(j-4)x^{i-j}y^{j-5} \end{aligned} \quad (21)$$

Now, we are ready to construct the linear system

$$Ac = b \quad (22)$$

is constructed such that  $A, b$  are matrices with 5 blocks:

1. The first one is constructed by satisfying the first boundary condition given in (2) using the formula in (17) for some given function  $u_0$  and for some selected points on  $\Gamma_1$ ,
2. The second block by satisfying the second boundary condition in (3) using the formula in (18) for some given function  $h_0$  and for some selected points on  $\Gamma_1$ ,



3. The third block by satisfying the third boundary condition in (4) using the formula in (19) for some given function  $w_0$  and for some selected points on  $\Gamma_1$ ,
4. The fourth block by satisfying the fourth boundary condition in (5) using the formula in (20) for some given function  $w'_0$  and for some selected points on  $\Gamma_1$ ,
5. The fifth block by satisfying the bi-Laplacian differential equation in (1) using the formula in (21) for some given function  $F$  and for some selected points in the domain  $\Omega \setminus D_\beta$ .

For this we select  $n_1$  points on the boundary  $\Gamma_1$ , say  $(x_i, y_i), i = 1, \dots, n_1$  to satisfy the condition (2-5) and we select  $n_2$  points in the domain  $\Omega \setminus D_\beta$ , say  $(x_j, y_j), j = 1, \dots, n_2$  to satisfy the equation (1). So the vector  $b$  is of order  $4n_1 + n_2$  and  $A$  is  $(4n_1 + n_2) \times n$  matrix and the vector  $c$  is of order  $n = \frac{m(m+1)}{2}$ .

$$A = \begin{bmatrix} v'_1 \\ \vdots \\ v'_{n1} \\ e'_1 \\ \vdots \\ e'_{n1} \\ d'_1 \\ \vdots \\ d'_{n1} \\ \varrho'_1 \\ \vdots \\ \varrho'_{n1} \\ \xi'_1 \\ \vdots \\ \xi'_{n2} \end{bmatrix} \quad b = \begin{bmatrix} u_0(\theta_1) \\ \vdots \\ u_0(\theta_{n1}) \\ h_0(\theta_1) \\ \vdots \\ h_0(\theta_{n1}) \\ w_0(\theta_1) \\ \vdots \\ w_0(\theta_{n1}) \\ w'_0(\theta_1) \\ \vdots \\ w'_0(\theta_{n1}) \\ 0 \\ \vdots \\ 0 \end{bmatrix} \quad (23)$$

So the inverse Cauchy problem for the bi-Laplacian equation is reduced to solve the linear system in (23).

## Solving the linear system by using CGM and CGLS algorithms

Consider the linear system given in (22), to solve this system, we use two well-known algorithms, which are the Conjugate Gradient method (CGM) and the Conjugate Gradient least square method (CGLS) (see [Rasheed et al., 2021], [Jameel et al., pre-print], [Hasan et al., pre-print]).

## Stopping criterion and Initial guess

An important thing that we need to care about to start and stop a numerical method, is that the initial guess (we take it the zero vector with a propitiate order) and for stop these algorithms is the following stopping criteria :





$$\|r_i\| < Tol \quad (24)$$

$$\frac{\|r_i\|}{\|b\|} < Tol \quad (25)$$

## 5 Numerical results and discussion

For illustrating the efficacy of the proposed method, we consider some examples with polynomial and non-polynomial exact solutions. The given exact solution is used to calculate:

- the function  $F$  in the domain  $\Omega \setminus D_\beta$
- the trace of the exact solution is equal to  $u_0$  on  $\Gamma_1$
- the normal derivative the exact solution is equal to  $h_0$  on  $\Gamma_1$
- the Laplacian of the exact solution is equal to  $w_0$  on  $\Gamma_1$
- the normal derivative of the Laplacian is equal to  $w'_0$  on  $\Gamma_1$

in addition to these data, we use the zero initial guess and the *CGM* and *CGLS* like-methods are used with some propitiate tolerance and stopping criteria.

### Example(1)

We consider the problem (1-5) with an exact solution is  $u(x, y) = x^4 - y^4$  with an annular domain bounded by  $\rho_e(\theta) = 1, \rho_i(\theta) = 0.5$ , the outer part of the boundary is the accessible part  $\Gamma_1$  is taken with  $\rho_e(\theta) = 1$  and  $\beta = 2$ , the number of points on the outer boundary is taken to be  $n_1 = 100$  and the number of the internal domain points is  $n_2 = 1000$ . We vary  $m$  from 2 to 10 for both algorithm *CGM* and *CGLS*.

$u(x, y) = x^4 - y^4$ when $n_1 = 100$ and $n_2 = 1000$ with $Tol = 10^{-10}$				
M	No. of Iteration for CGM	Relative Error with CGM	No. of Iteration for CGLS	Relative Error with CGLS
2	-	-	-	-
3	-	-	-	-
4	-	-	-	-
5	2	1.8e-12	3	2.1189e-12
6	2	9.8e-12	4	3.2864-12
7	8	6.3e-09	8	0.22957
8	11	3.6e-09	12	0.22957
9	23	1.5e-07	17	0.0094068
10	28	2.7e-08	18	0.0094068
11	45	0.00042	36	0.32837



We note that when we take  $m = 2,3,4$ , the both algorithms do not attend an accepted accuracy of convergence. The exact solution is a polynomial of degree 4, so the ideal approximation obtained for  $m = 5$ , i.e. we approximate a polynomial of degree 4 by a polynomial of degree 4, so when we take  $m = 5$ , the convergence is attended with 3 iterations with a relative error **2.1189e-12** for CGLS and with 2 iteration with a relative error **1.8e-12** for CGM which are very ideal.

Now we take the case with  $n_1=400$  and  $n_2=8000$ ,  $Tol = 10^{-10}$

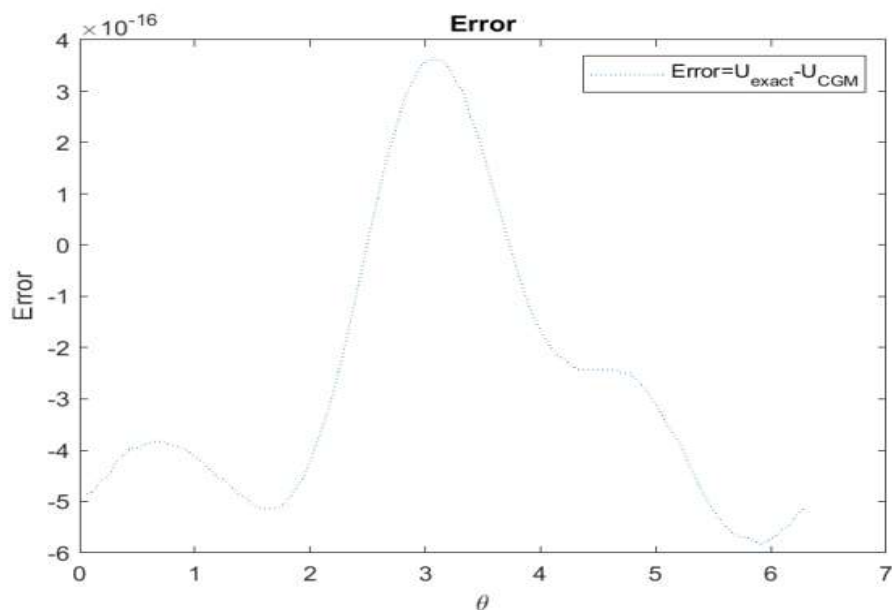
<b><math>u(x, y) = x^4 - y^4</math> when <math>n_1=400</math> and <math>n_2=8000</math>, <math>Tol = 10^{-10}</math></b>				
M	No. of Iteration for CGM	Relative Error with CGM	No. of Iteration for CGLS	Relative Error with CGLS
2	-	-	-	-
3	-	-	-	-
4	-	-	-	-
5	<b>2</b>	<b>3.7e-12</b>	<b>3</b>	<b>4.4697e-14</b>
6	3	2.7e-12	4	1.4576e-11
7	9	2.4e-10	10	0.22957
8	11	2.6e-09	15	0.22957
9	24	5.6e-08	17	0.0097726
10	32	9.4e-09	27	0.0097726
11	55	0.00042	42	0.033654

Similarly to the previous case, we note that when we take  $m = 2,3,4$ , the both algorithms do not converge. In fact, our exact solution is a polynomial of degree 4, so the ideal approximation obtained for  $m = 5$ , i.e. we approximate a polynomial of degree 4 by a polynomial of degree 4, so when we take  $m = 5$  the number of iteration equal to 4 and the relative error is equal 4.4697e-14 for CGLS and 3.7e-12 for CGM which are very ideal.

The following figures show the errors and the comparison of the exact solution and the approximate solution calculated by CGM.

In the following the figure of the exact and approximate solutions by CGM and CGLS.

In the following the error by CGM.



**Figure 2:** Error by CGM for  $n_1=100$  and  $n_2=1000$  with  $Tol=10^{-10}$

### Example(5.2):

In this example we suppose that the exact solution is  $u(x, y) = x^4 + y^4$  the domain is bounded by  $\rho(\theta)=1$  and  $\Gamma_1$  is defined taking  $\beta=2$  the number of boundary collection used for discretizing the boundary is taken to be  $n_1=100$  and  $n_r=10$  and the number of internal collection  $n_2 = 1000$ .

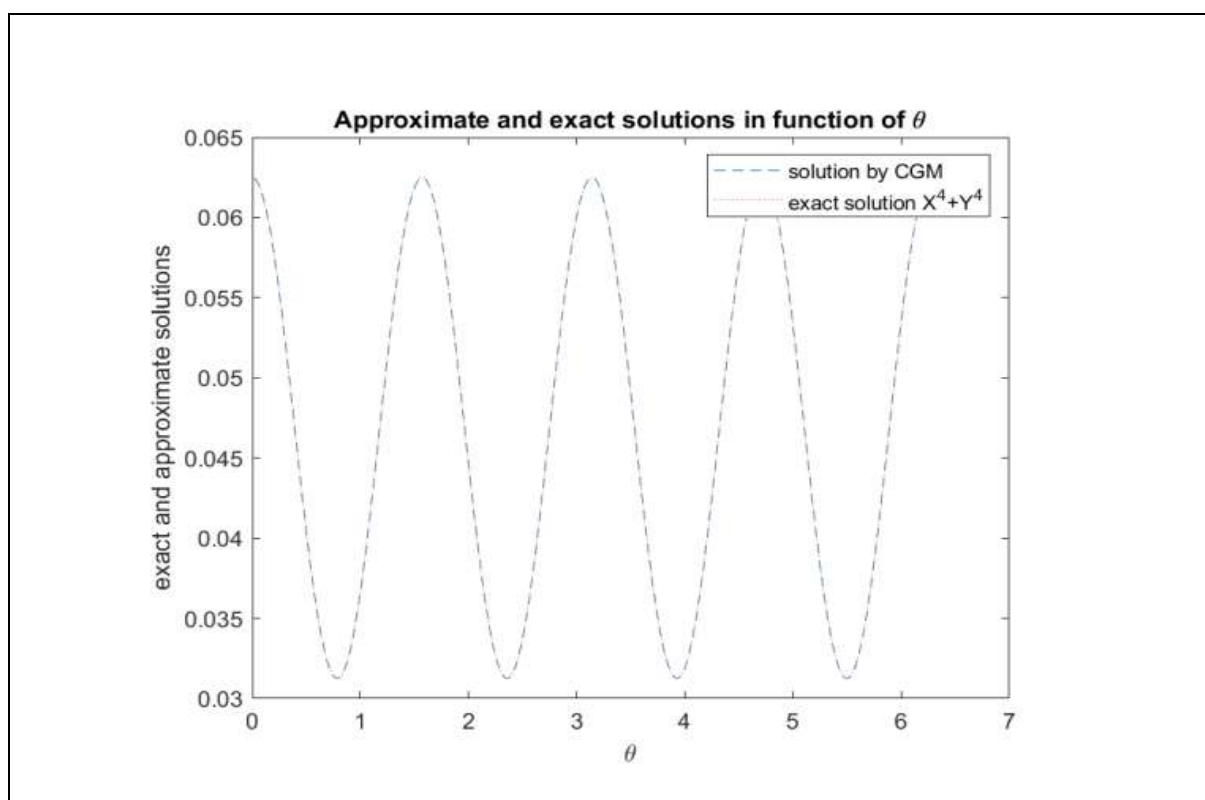
Case 1:  $n_1=100$  and  $n_2=1000$  with  $Tol = 10^{-10}$

$u(x, y) = x^4 - y^4$ when $n_1 = 100$ and $n_2 = 1000$ with $Tol = 10^{-10}$				
M	No. of Iteration for CGM	Relative Error with CGM	No. of Iteration for CGLS	Relative Error with CGLS
2	-	-	-	-
3	-	-	-	-
4	-	-	-	-
5	6	5.6678e-14	3	2.1189e-12
6	11	6.4118e-13	4	3.2864e-12
7	20	1.6091e-12	8	0.22957



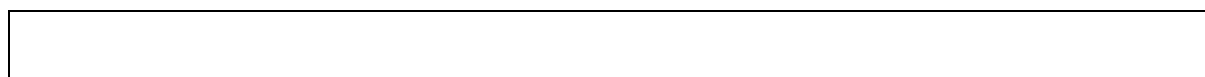
8	27	2.4387e-12	12	0.22957
9	88	9.3526e-10	17	0.0094068
10	126	1.2239e-09	18	0.0094068

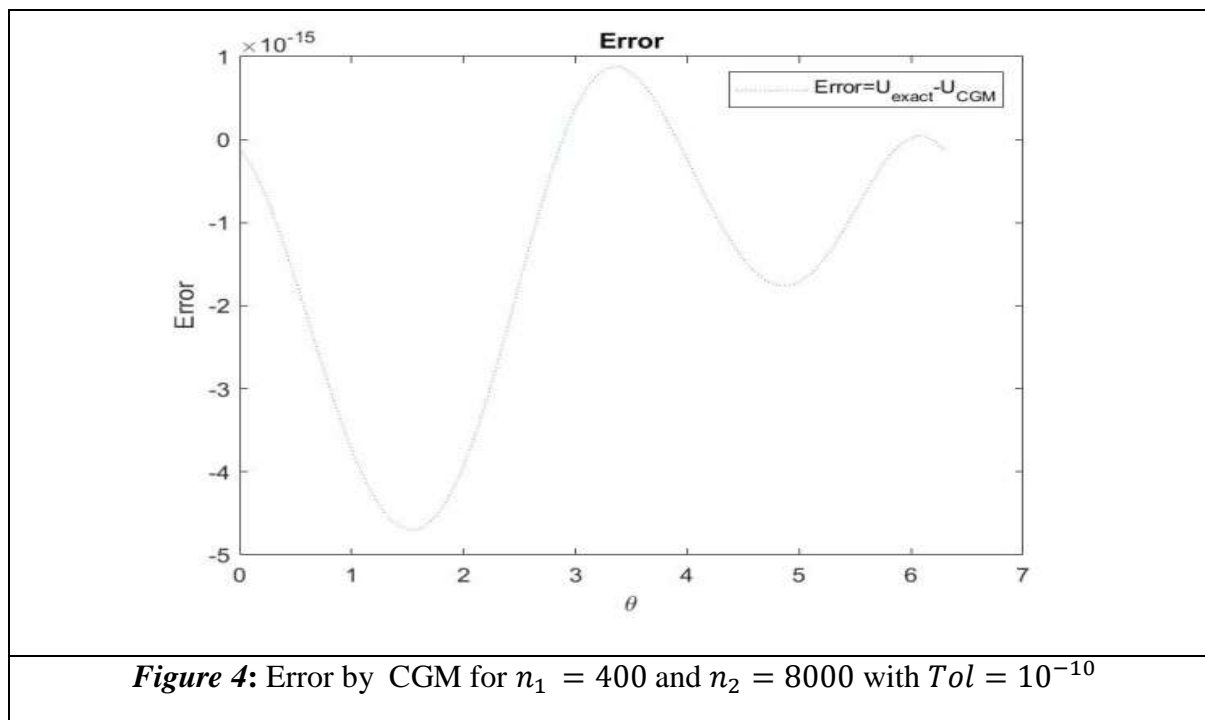
For  $m=5$  the number of iteration =6 and the relative error is equal **5.6678e-14** for CGM and **2.1189e-12** for CGLS that is a good approximation.



**Figure 3:** Approximate Solution by CGM and exact solution  $u(x, y) = x^4 + y^4$  for  $n_1 = 400$  and  $n_2 = 8000$  with  $Tol = 10^{-10}$

In the following the figure of the error:





**Example(5.3):**

In this example we solve the problem (1-5) by supposing that the exact solution is

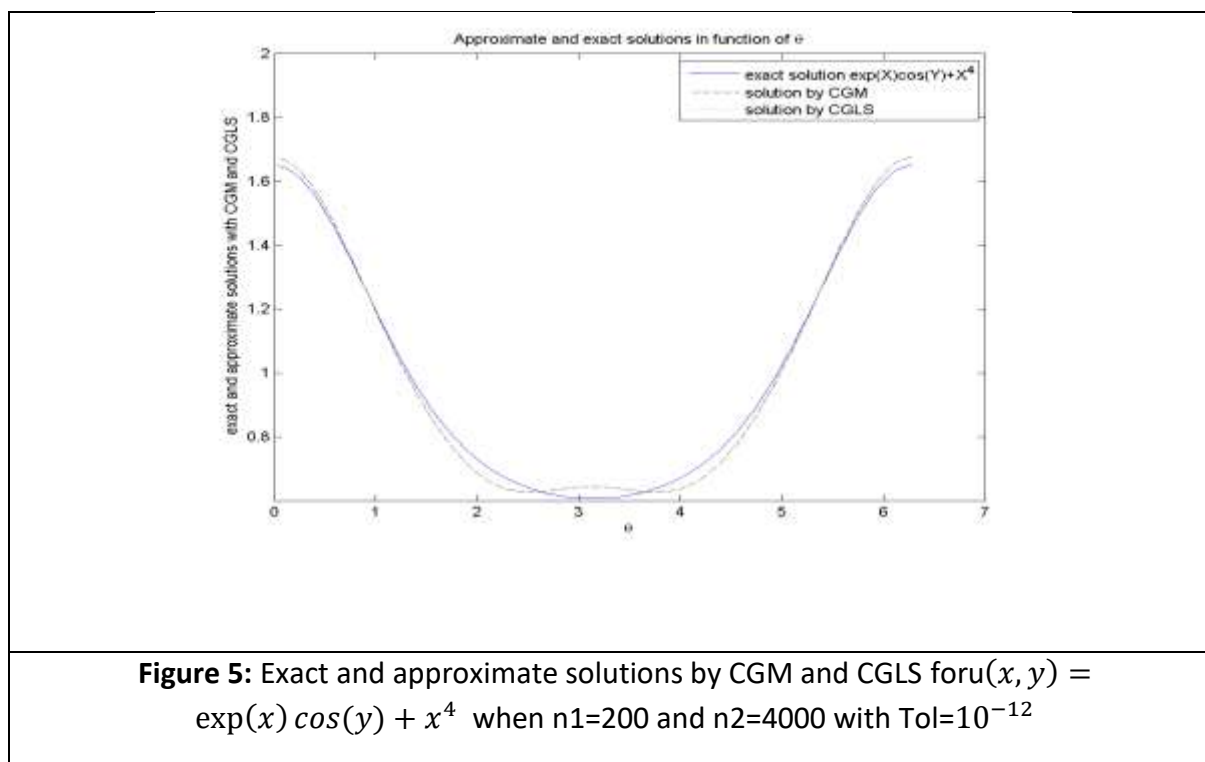
$$u(x, y) = \exp(x) \cos(y) + x^4$$

with the same domain and boundary for the previous examples .The number of boundary on the boundary is taken to be  $n_1 = 200$  and the number of the points in the interior domain is  $n_2 = 4000$ . As the previous examples we study the cases of  $m = 2, \dots, 11$ ,for both CGM and CGLS algorithms, with a tolerance  $Tol = 10^{-12}$ .

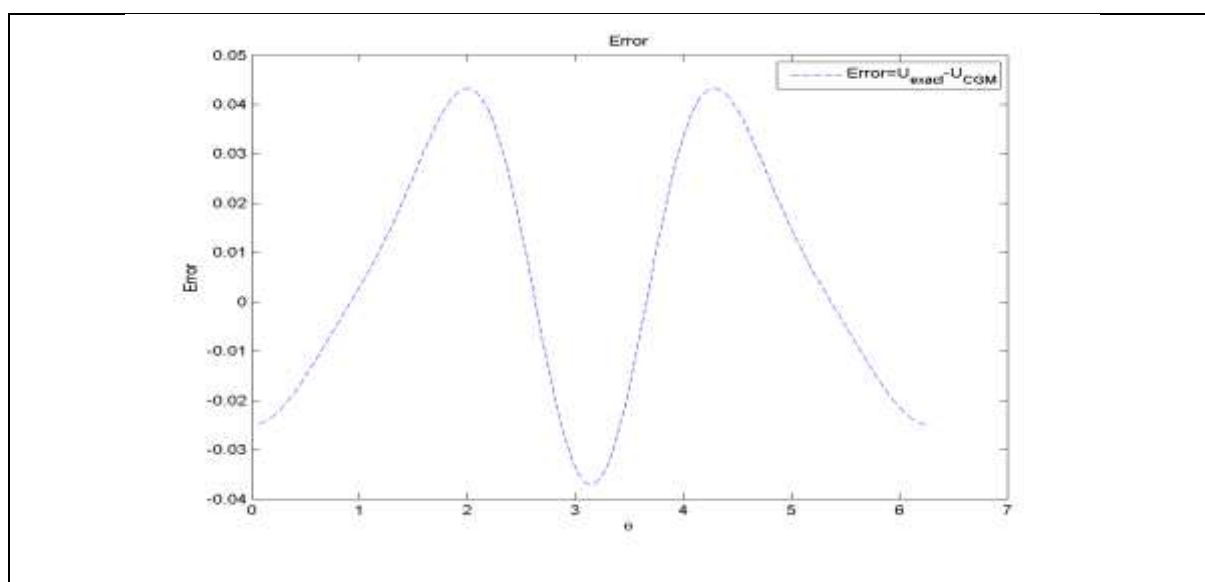
$u(x, y) = \exp(x) \cos(y) + x^4$ when $n_1 = 200$ and $n_2 = 4000$ with $Tol = 10^{-12}$				
M	No. of Iteration for CGM	Relative Error with CGM	No. of Iteration for CGLS	Relative Error with CGLS
2	-	-	-	-
3	-	-	-	-
4	-	-	-	-
5	13	0.026025063244862	13	0.026025063245107
6	21	0.0245600183899321	25	0.024560018387322
7	<b>43</b>	<b>0.023827973140670</b>	<b>44</b>	<b>0.023827973190222</b>
8	73	0.032073059303643	76	0.032073059309326

9	172	0.032816995991338	154	0.032816994769686
10	370	0.032398126449167	312	0.032398123460117

In the following the figure of the exact and approximate solutions by CGM and CGLS.

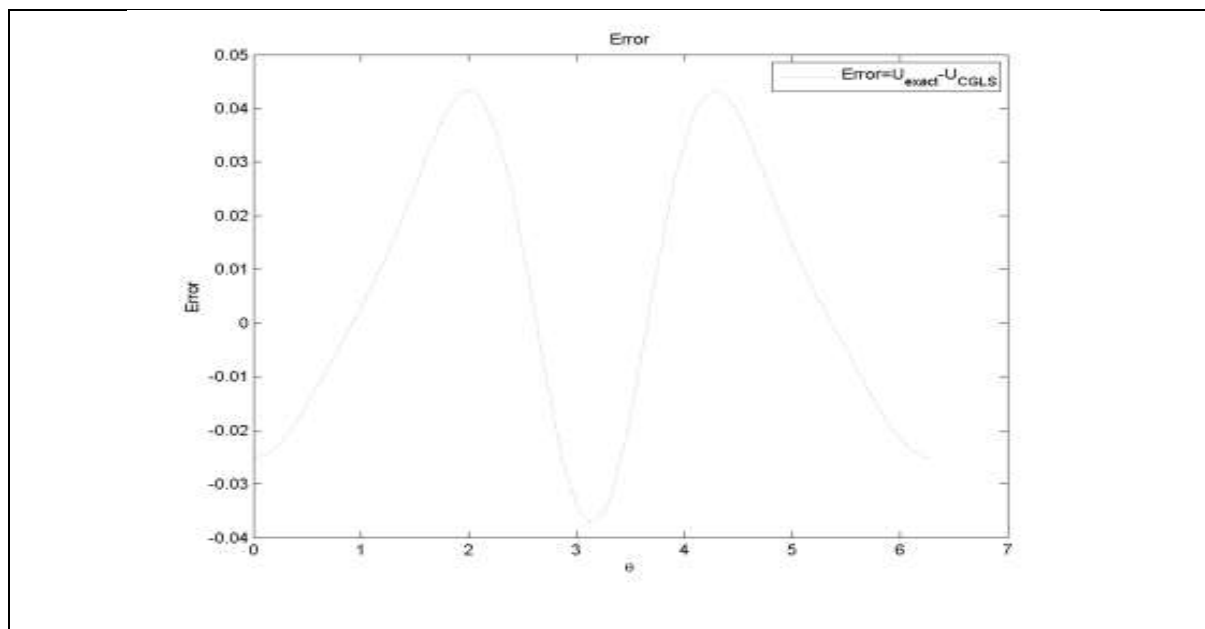


In the following the error by CGM.



**Figure 6:** Error between exact solution and the calculate approximation by CGM

In the following the figure of the error CGLS.



**Figure 8:** Error between exact solution and the calculate approximation by CGLS

## 6 Stability and effect of a noise

It is well-known that the inverse problem depends on the data that may have some error due to the measurement error. So, we check the effect of any noise of the data on the calculate solution. Here, we give the following form of the noise on the Cauchy data:

$$u_0(\theta) = u_{ex}(\rho, \theta) + \sigma * rand$$

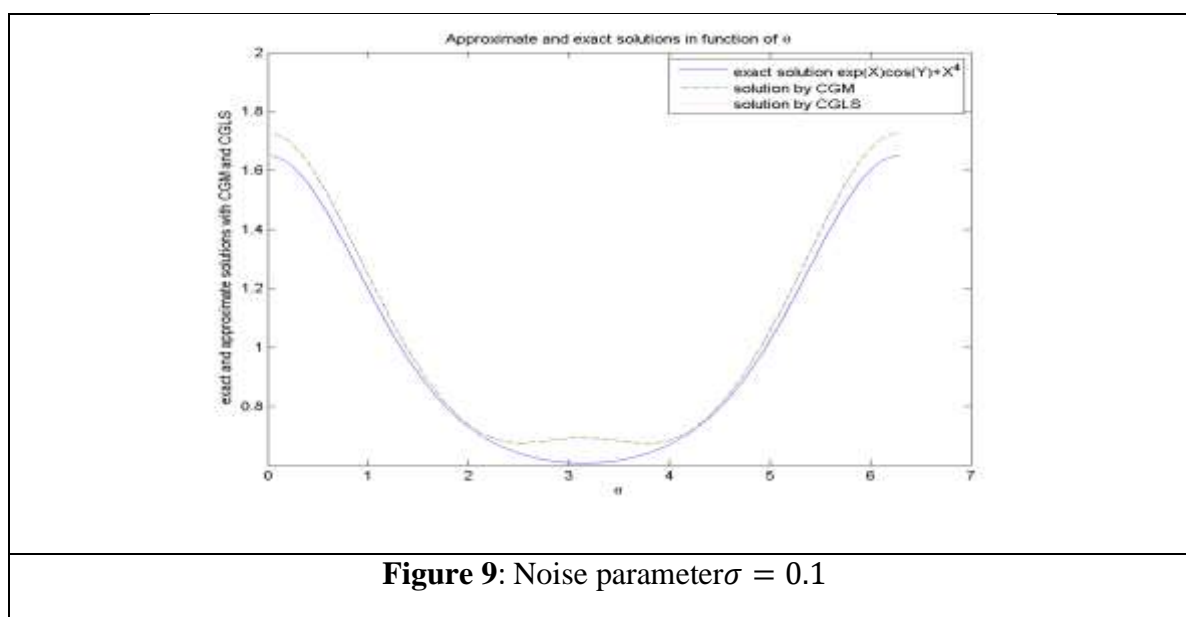
Where *rand* is the Gauss random error and  $\sigma$  is the deviation of measurement errors.  $\sigma$  is the noise level, it takes the values 0.001, 0.01, 0.05 and 0.1.

We test the effect of the noise for example 3.

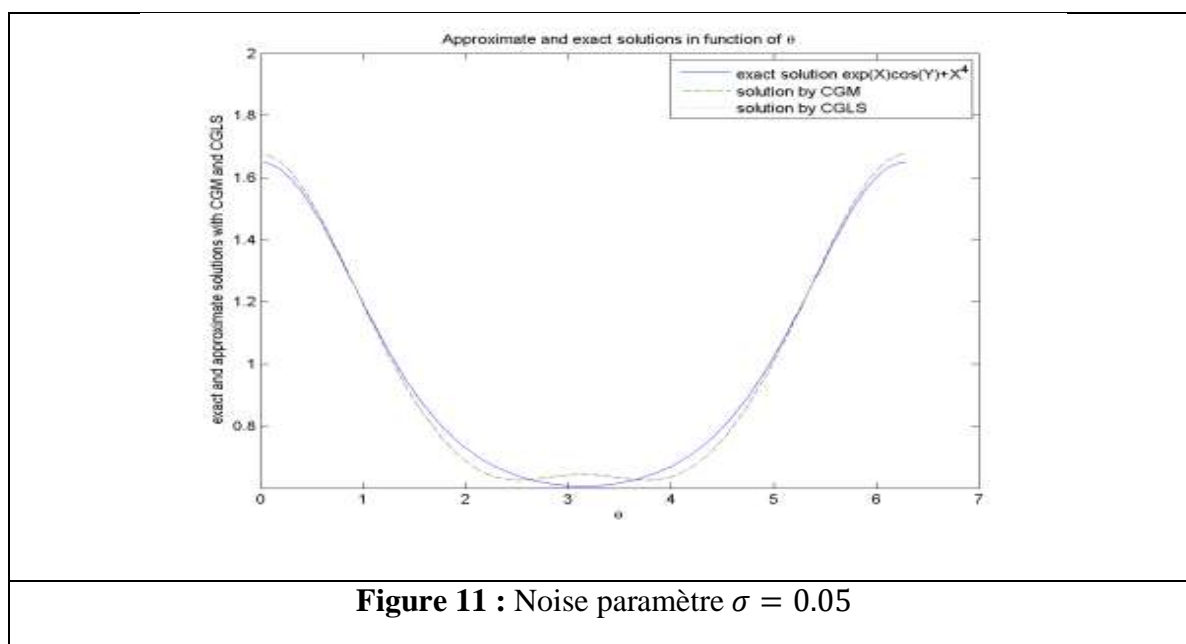
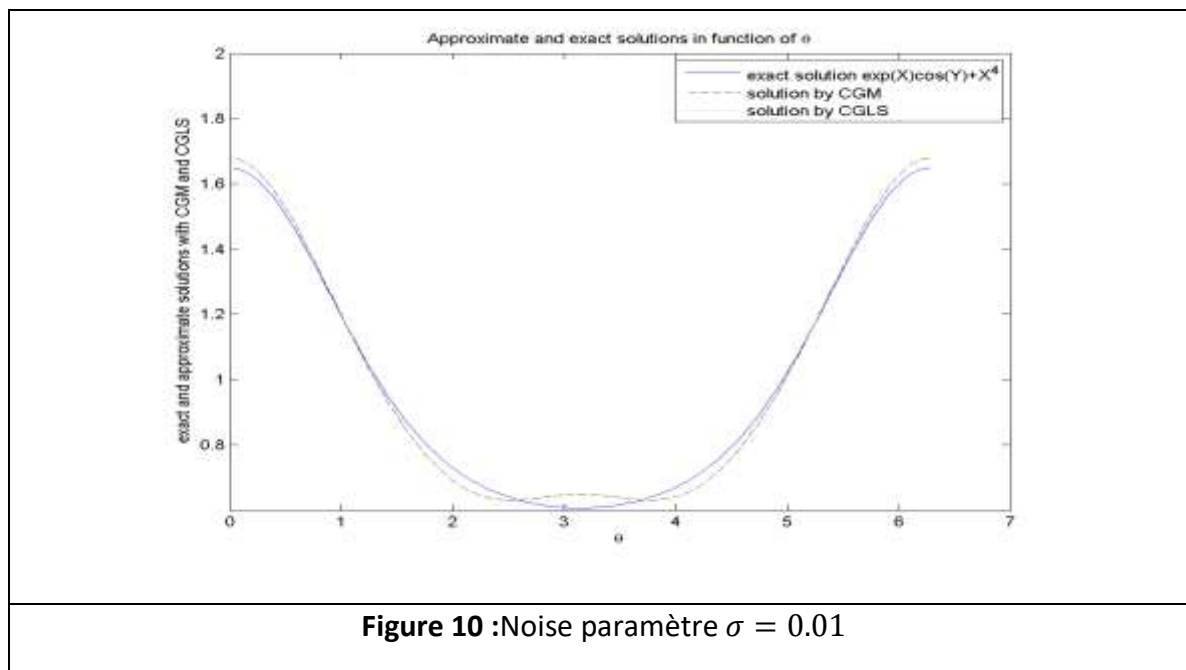
$u(x, y) = \exp(x) \cos(y) + x^4$ when $n_1=200$ and $n_2=4000$ with $Tol = 10^{-12}$				
$\sigma$	No. of Iteration for CGM	Relative Error with CGM	No. of Iteration for CGLS	Relative Error with CGLS

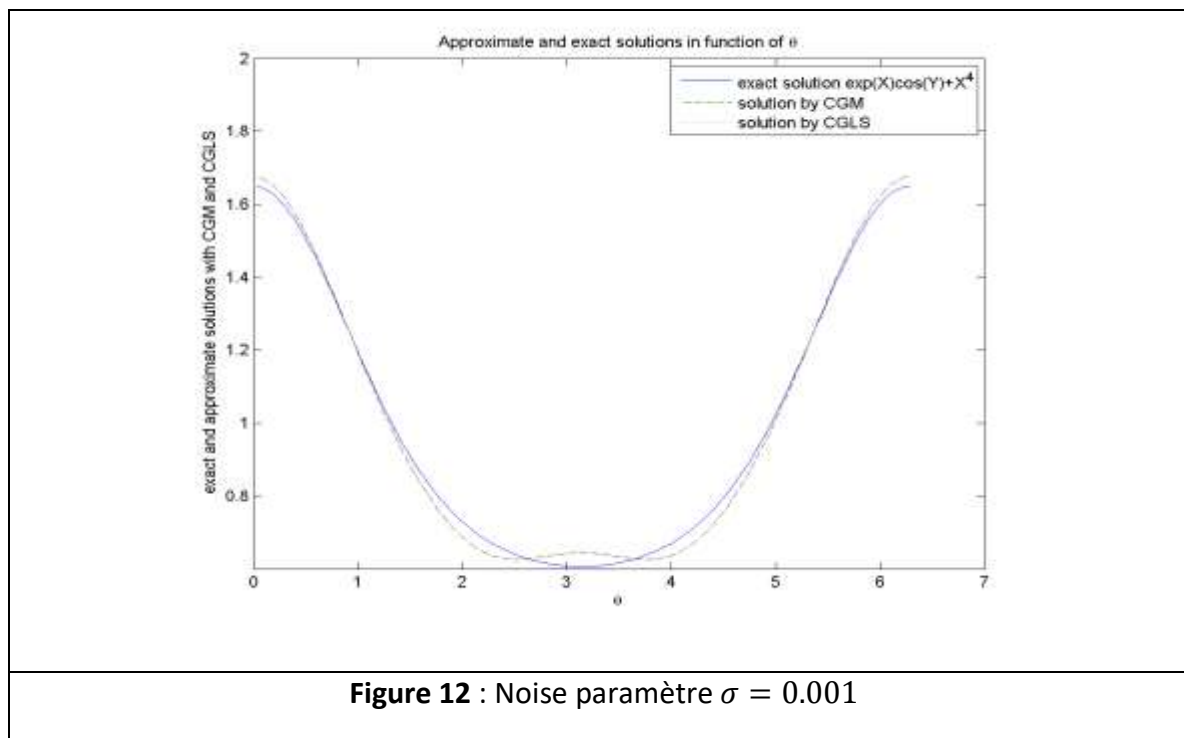
<b>0.1</b>	<b>58</b>	0.048048673438369	<b>61</b>	0.048048673438261
0.01	61	0.023294161460917	65	0.023294161455813
0.05	60	0.029669222287058	62	0.029669222287195
0.001	57	0.023741709140837	64	0.023741709141370

In the following the figures of each case:









In fact, the problem in example 3 is ill-posed with Condition number about  $2.355744917801085e+003$ . Figures present the exact and calculate approximate solutions obtained by both CGM and CGLS on the boundary  $\Gamma_2$ . These figures show that for a big value  $\sigma = 0.1$  the approximate solution move away from the exact solution and the error multiplied by 2 and by reducing the value of  $\sigma$  until  $\sigma = 0.001$  the approximate solution be closer to the exact solution, the most important for all these cases the solution still stable for both CGM and CGLS. These both approximations still good, even for a high value of noise until  $\sigma = 0.1$  relative random parameter, in fact our problem is highly ill-conditioned with condition number  $2.355744917801085e+003$ .

## 7 Conclusion

We solve the inverse Cauchy problem of bi-Laplacian differential equation in an annular domain, the unknown data on a part of the boundary are recovered from the over-specified Cauchy boundary conditions. The inverse Cauchy problem is reformulated to solve a direct problem benefiting from a polynomial expansion of the solution. Different kind of numerical examples with polynomial and non-polynomial exact solution are presented to confirm that our proposed method overcome the severe ill-posedness of the inverse Cauchy problem. The stability of the method is checked by applying a different value of noise on the Cauchy data.

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## تحضير ودراسة الاهمية الدوائية لمشتقات Isoxazoline : مقالة مراجعة

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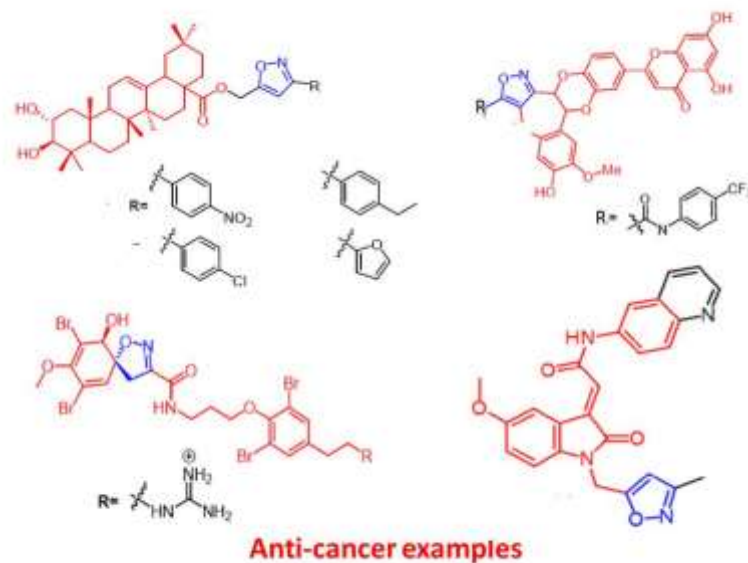
### الخلاصة

المركبات الحلقية الخماسية الغير متجانسة الحاوية على الاصرة (C=N-O) مثل الايزوكسازولين تمتلك العديد من الصفات العضوية الحيوية والصيدلانية. كما أنها تعتبر مركبات وسطية مهمة في الكيمياء العضوية. من خلال الدراسات العلمية فانه من المعروف ان هذا النوع من المركبات غير المتجانسة له العديد من الفعاليات البيولوجية. لذلك في هذه المقالة، تمت مراجعة العديد من طرق ومسارات التصنيع لهذه الجزيئات التركيبية نحو أنظمة فعالة حيويًا تمتلك تطبيقات طبية متقدمة ومتنوعة. وصفت الكثير من الدراسات البحثية ومقالات المراجعة مسارات تحضير مشتقات الايزوكسازولين والتي تمثل مصفوفة متنوعة اتجاه تطور هذا القالب المهم وتفقد هذا المركز الى تحديثات مستقبلية نحو الحصول على معالجات آمنة واكثر فعالية.

**الكلمات المفتاحية:** المركبات الحلقية الغير متجانسة ، الايزوكسازولين، الفعالية البيولوجية، الفعالية المضادة للسرطان، الفعالية المضادة للأكسدة.

### Introduction

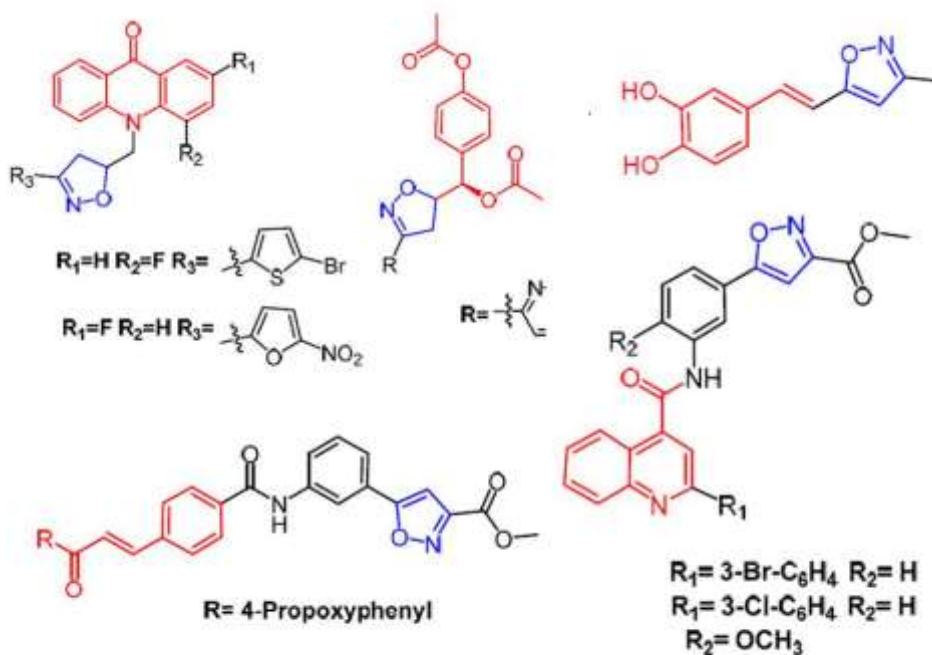
Isoxazolines in medicinal chemistry are synthetic and natural occurrence compounds (Figures 1&2). They have pharmacological treatments role in the treatment of some conditions like inflammatory, cancer, bacterial, fungal, parasitic, Alzheimer, insecticidal and diabetic [1- 6].



**Figure 1:** Isoxazoline derivatives with anti- cancer activity [6].

In research field, 1,3-dipole cycloaddition reactions generate derivatives containing this moiety even with modification of natural products. These hetero (Nitrogen and Oxygen) partially saturated compounds with electron-rich structural candidates are

of particular intermediates. These unique architected compounds have a high affinity binding with complementary receptors that assisted target therapeutic applications.



## Antimicrobial examples

**Figure 2.** Antimicrobial examples having isoxazoline moiety [6].

Natural isoxazoline backbone exhibits remarkable activity that is demonstrated by number of studies. However, natural components extraction, isolation then modification pointed direct usage for trial reports and clinical treatment with high pharmacological activity and physicochemical properties where their biological activity reduces side effects and improves selectivity [1,3],[7-11].

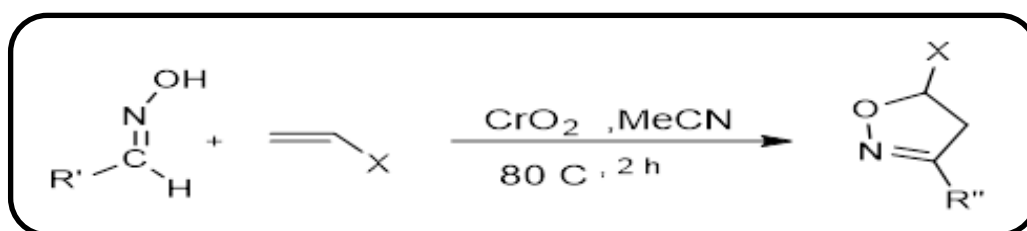
A highly appreciable number of five-membered heterocycles, containing nitrogen - oxygen bond compounds have turned out to be potential chemo- and pharmaco- therapeutic agents. Synthetic analogs of this hetero nucleus with therapeutic properties can be obtained through of lead compound relationship. Isoxazolines derivatives like other cyclic compounds systems show cis-trans structural isomerism where four stereoisomers are possible for isoxazolines containing identical substituents at C3 and C5 positions. These are the two *cis*- and two *trans*-forms [12].



A lot of modifications were added to isoxazoline molecules during the last few years, and chemical and biological activities of these derivatives were studied during the last few years on isoxazoline molecules and chemical and biological activities of these derivatives have been studied. Isoxazoline derivatives were converted into different classes of heterocyclic molecules with different types of potential biological activities including antimicrobial, antiinflammatory, fibrinogen receptor and glycoprotein receptor antagonist, anticancer, anti-HIV, and antidepressant activities beside insecticidal, antibiotic, anti-tumor, anti-tuberculosis and ulcerogenic properties [11]. Because of these applicable importance, this study aimed to cover more important synthetic approaches to isoxazoline derivatives and their reactivities to increase researchers' interest in this scaffold in organic synthesis.

### Summary of synthesis methods:

- a. Quilico experiment: The reaction of Nitrile oxides with unsaturated compounds is the first path of isoxazole chemistry [13].
- b. Huisgen cycloaddition: Nitrile oxides introduced in this synthetic method of isoxazolines as an example of 1,3-dipolar cycloaddition reactions [14,15]. The alkene reacts with nitrile oxide in situ mechanism in moderate yields (Scheme - 1). The method has proven to be just as versatile for intramolecular nitrile oxide cycloaddition reactions [16].

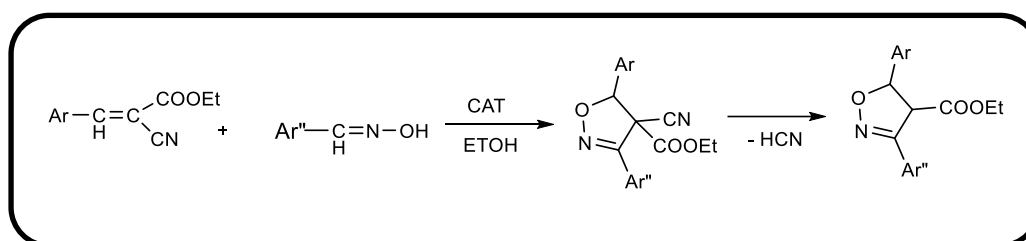


**Scheme 1:** Efficient synthesis of the target heterocycles from aldoximes using Magtrieve (CrO<sub>2</sub>)

- c. Oxidative dehydrogenation of aldoxims:, The nitrile where reacted with unsaturated ester substituted with nitrile group to produce ethyl 3,5-diaryl isoxazole-4-carboxylates. It was

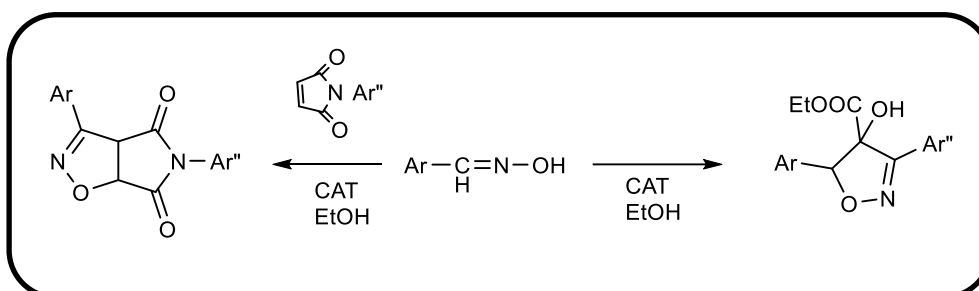


observed that peculiar reaction conditions were done for careful removal of HCN from their predicted cycloaddition reaction (CAT) isoxazolines[17]. (Scheme-2)



**Scheme 2:** Synthesis of cycloaddition isoxazolecompined by HCN removal.

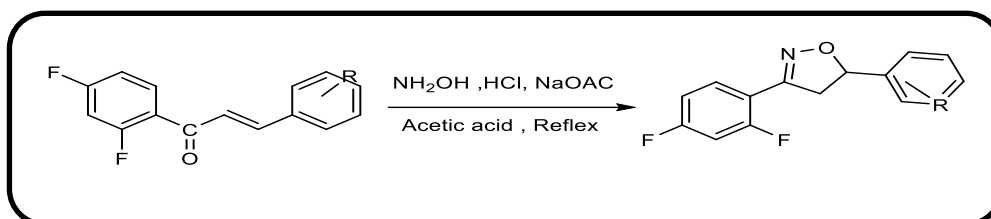
Scheme - 3 is a good example of 1,3-dipolar cycloaddition of N-aryl maleimides towards a series 3-Aryl-5N-aryl-4,6-dioxo-pyrrolo[3,4-d]-7,8-dihydroisooxazolines via a dipolarophile to obtained the substituted isoxazolines in a good yield[18].



**Scheme 3:** Isoxazoles synthesis via 1,3-dipolar cycloaddition.

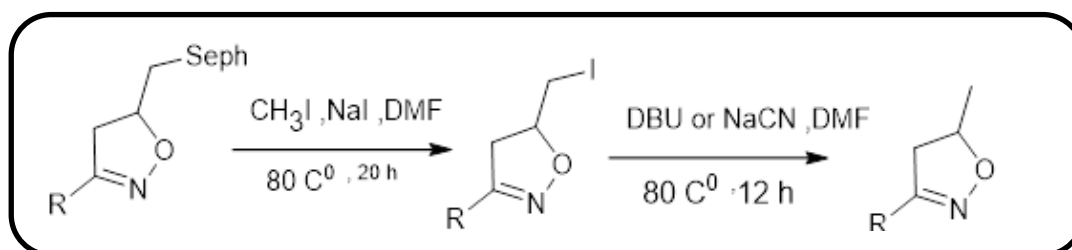
**d. Condensation reaction:** Three component condensation reaction in free solvent - basic medium is considered a favored path like synthesis of 4-Arylidene-3-phenylisoxazol-5-ones via combination of aromatic aldehyde in the same reaction vessel with ethyl benzoylacetate, hydroxylamine, and 1,4-diazabicyclo[2.2.2]octane (DABCO) under reflux condition [19] .

Fluorinated chalcones condensation with hydroxylamine in acidic medium was another example of isoxazoline preparation under reflux conditions (Scheme-4). The evaluation of the final products in bacterial resistance section showed a good activity where fluorine presence altered valuable stability and lipophilicity characters towards good biological activity [20].



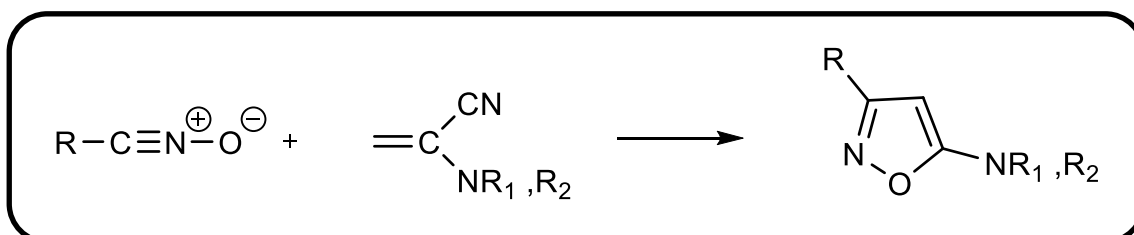
**Scheme 4:** Condensation reaction towards fluorinated derivatives

- e. deselenenylation reaction: Wei Ming *et. al.* presented another isoxazoline derivatives functionalized by 3, 5 – substitution sites where aromatic selenide of isoxazoline derivative produced their substituted isoxazoles (Scheme-5) in basic medium [21].



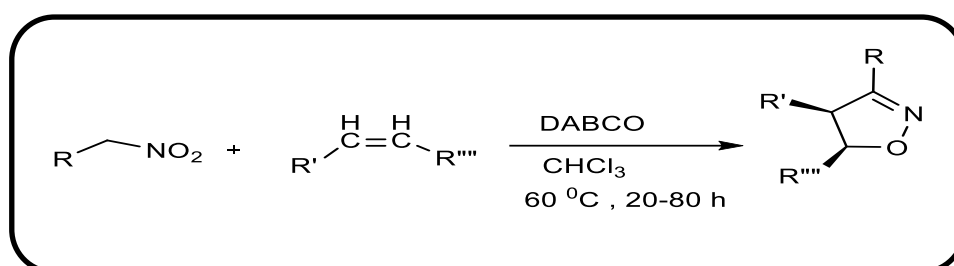
**Scheme 5:** Deselenenylation reaction to synthesis of disubstituted isoxazole and isoxazoline with use of 1,5-diazabicyclo [5,4,0]-undec-5-ene (DBU) or NaCN as a base under reflux condition.

- f. One-step regioselective - 1,3-dipolar cycloaddition reaction: A quick, efficient and easily One-step regioselective - 1,3-dipolar cycloaddition reaction was performed to prepare 5-aminoisoxazoles using nitrile oxides and  $\alpha$ -cyanoenamines (Scheme-6) [22].



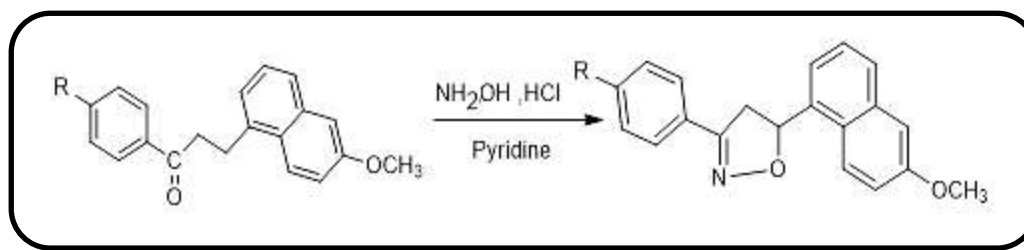
**Scheme 6:** One step synthesis of 5-aminoisoxazoles via 1,3-dipolar cycloaddition.

- g. Dehydration reaction of primary nitro compound:** In the reaction mixture aldoxims with 4-methoxy cinnamionitrile provided 1,3-Dipolar cycloaddition reaction converted to isoxazolines where dipolar primary nitrophiles (nitro compound) with 1,4-diazabicyclo[2.2.2]octane (DABCO) base presence. The reaction of activated nitro compounds affords isoxazoline in excellent yields compared to other methods (Scheme-7) where nitro alkanes have low reactivity [23]



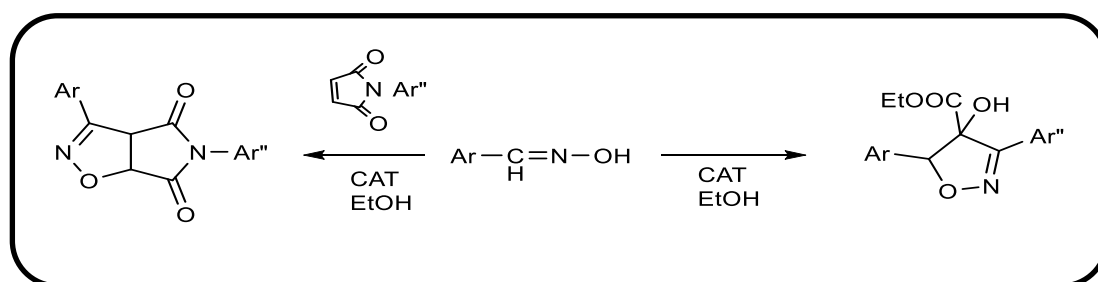
**Scheme 7:** Preparation of phenylisoxazol-5-one derivatives.

By returning to chalcone reaction, many isoxazoline derivatives were synthesized with fast reaction with hydroxylamine.HCl- NaOH mixture. Mannich bases and substituted primary amines (hydroxylamine. HCl) were reacted with substituted phenyl ketone under reflux conditions to produce a series of substituted methoxynaphthalene)-2-isoxazolines (Scheme 8) having a significant to moderate antimicrobial activity. [24]



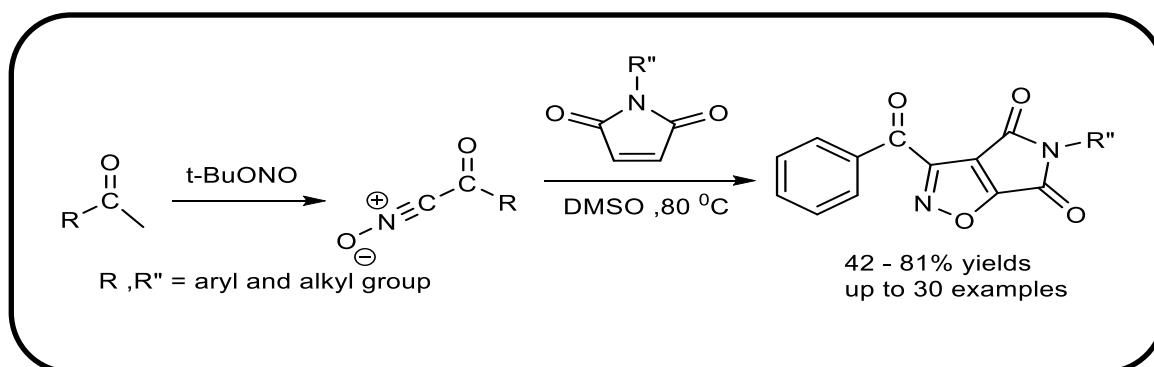
**Scheme 8:** Synthesis of some novel Mannich bases of isoxazolines.

The prepared cyclic nitrile oxide (or substituted isoxazolines) like Pyrrolo[3,4-d]-7,8-dihydroisooxazolines via in situ 1,3-dipolar cycloaddition of N-aryl maleimides were introduced in reaction with acetyl acetone towards novel pyroazolines with same mechanism of reaction (Scheme – 9) [25].



**Scheme 9:** Some novel pyrazoline- isoxazolines by 1, 3 cycloaddition (CAT) of N- aryl imides.

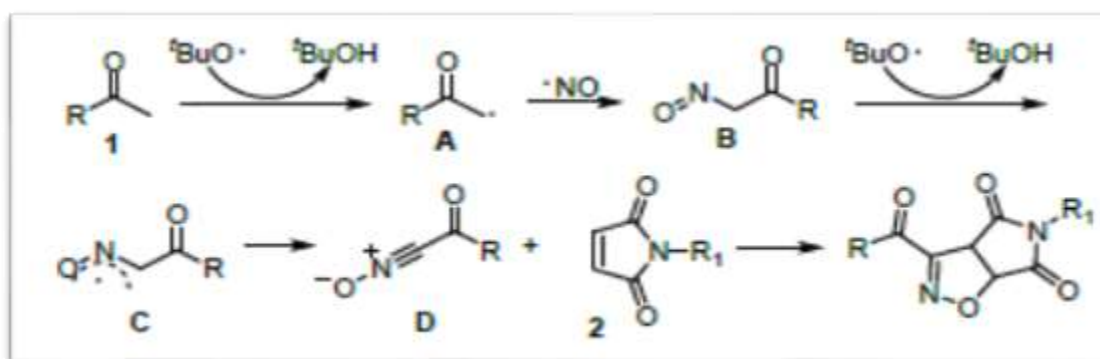
- h. Cycloaddition of ketone, O- alkyl nitrite and maleimide (1,3-dipolar cycloaddition reaction)** (Scheme 10):\_An effective approach in the subject of isoxazole and isoxazoline derivatives were constructed by nitrile oxides, alkynes or alkenes bound to a resin and performed on solid supports bonded (Ar) or (alkyl) building blocks with some limitations in structural diversity[26]. Also, substituted pyrrolo [3,4-d] isoxazolines have been synthesized with absence of metallic catalyst [27].



**Scheme 10:** One-pot radical - cycloaddition of alkyl ketone by tert-Butyl nitrite (t-BuONO), and N- substituted maleimide

Mechanism of this constructed reaction (Scheme -11) was confirmed by X-rays crystallography, and it was the generation of tert-Butyl nitrite (t-BuO) radical from tert-butyl nitrite, subtraction of methyl hydrogen in methyl ketone, providing a radical (A) centered at carbon atom, attacking of NO radical to radical carbon and producing nitrosoketone (B), then reacting with t-BuO radical presented acyl nitrile oxide (D).

This mechanism ended by 1,3-dipolar cycloaddition of (D) and N- substituted maleimide towards pyrrolo[3,4- d]isoxazoline product. DMSO as a good solvent and abstracter hydrogen atom that required lower energy compared to t-BuO radical [28].



**Scheme 11:** Mechanism details of hydrogen abstraction – cycloaddition towards pyrrolo[3,4- d]isoxazolines.

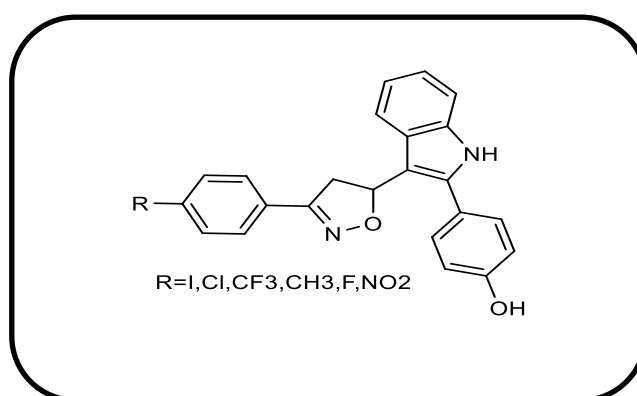
- i. Three-Component 1,3-Dipolar Cycloaddition by Spirooxindole-Fused with Triazole: Acetophenone reaction with aryl nitrile and aryl azide yielded isoxazoline and isoxazole cycles combined by spiro-oxindoles or triazole using Cu (I) as a catalyst. X-rays diffraction verified the regiochemistry and stereochemistry while various antibacterial and antifungal testing confirmed biological behavior of the resulted derivatives compared to conventional medicines [29].

Discovering and development of antimicrobial agents are goals of scientific community now days with high ability to resist known infections through multi-step, multi-components, one - pot and combinational chemistry [30] towards effective therapies [31]. These powerful tools in

organic and medicinal chemistry [32] are targeting simplicity in reaction conditions and economy especially in N-heterocyclic synthesis with high regio – stereo selectivity, environmental mode, time and yield.

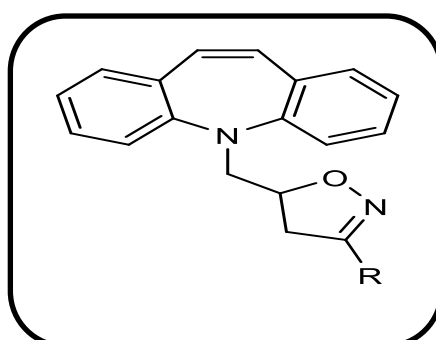
## Pharmacological effect of isoxazoline and its derivatives

A new series of phenol – isoxazolines derivatives was synthesized and their analgesic effects were testing [33], Figure 3.



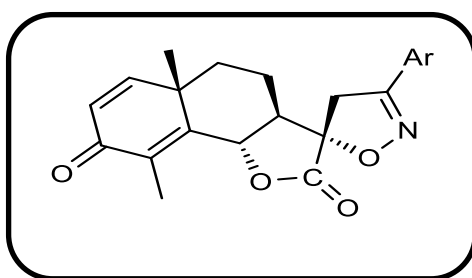
**Figure 3:** Indole derivatives linked to isoxazole moiety.

New dibenzoazepine isoxazoline with Dibenzoazepine cycle was synthesized, characterized by 2D NMR, then their biological inhibition or resistance effects were compared to cisplatin and suramin in murine osteosarcoma cells (LM8G7), human ovarian cancer cells (OVSAHO) breast cancer cells (MCF-7), and Myeloma cells (RPMI8226-LR5) [34], Figure 4.



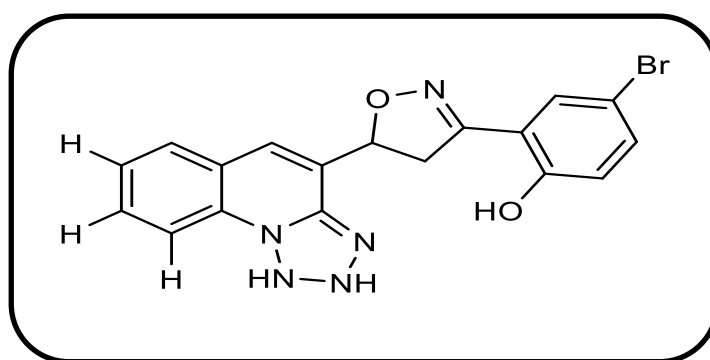
**Figure 4:** Chemical structure of dibenzo[b,f]azepine – N- linked isoxazoline derivatives.

1,3-dipolar cycloaddition was the applied path in generation of lactone linked to isoxazoline or isoxazolidine ring and their anticancer activity of these novel spiro derivatives related to prostate cancer cell (PC-3) and MCF-7 cell lines were evaluated with (0.01- 0.3) mM [35], Figure 5.



**Figure 5:** Spiro-isoxazoline derivatives having good anticancer activity.

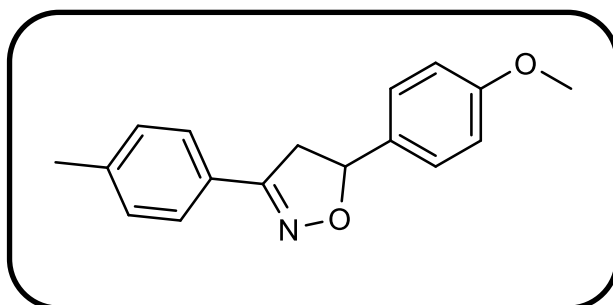
Nikam research team [36] synthesized a series of isoxazolines by applying sonochemistry field, starting from chalcones. The *in vitro* microbial behaviors, molecular docking and antioxidant of these isoxazolines with the 2,2-diphenyl-1-picrylhydrazyl (DPPH) were performed, Figure 6.



**Figure 6:** Structure of isoxazoline derivated from chalcone.

Isoxazoline derivatives based on chalcones were prepared from substituted benzaldehyde and substituted acetophenone, condensed with  $\text{NH}_2\text{OH} \cdot \text{HCl}$  then selected to evaluate *in vitro*

antibacterial studies against (*S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*) and antioxidant - DPPH radical scavenging [37], Figure 7.

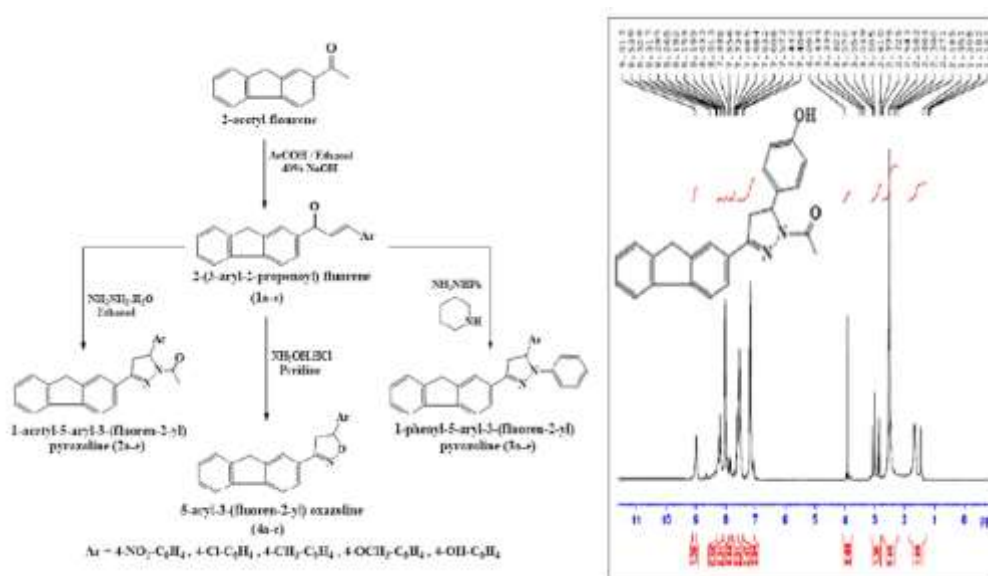


**Figure 7:** New Indolo[3,2-c]isoquinoline having very good activity against *P. aeruginosa*.

Thirty isoxazoline derivatives including 3,5-substituted-4,5-dihydroisoxazoline and 3,5-substituted aryl-4,5-dihydroisoxazoline were prepared by  $\text{H}_2\text{SO}_4$  catalyzed cyclization of hydroxylamine hydrochloride and aryl chalcones under solvent-free conditions. The antimicrobial, antioxidant and insecticidal activities of the synthesized isoxazolines were evaluated [38].

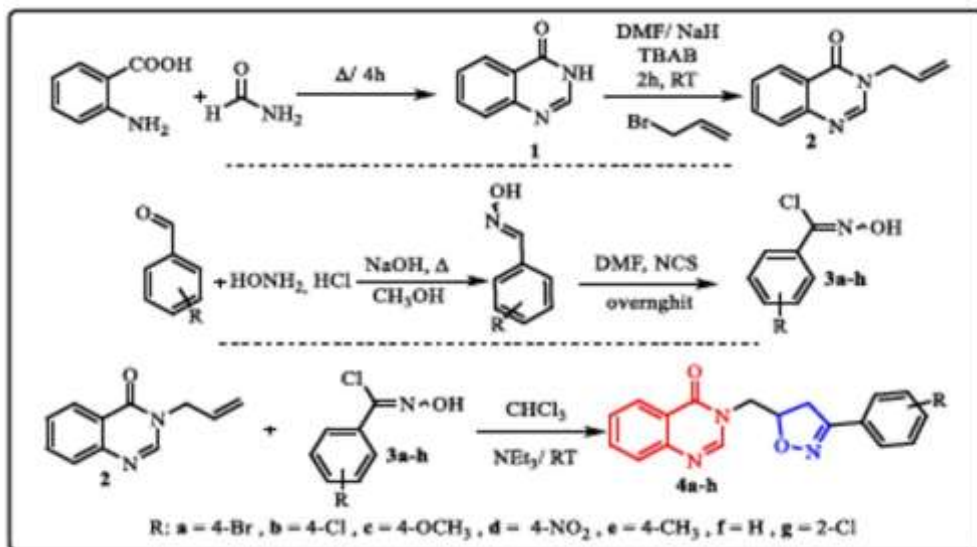
Synthesis of new heterocyclic fluorene – Isoxazoline derivatives were made up from 2-acetyl fluorene with aromatic aldehyde in basic medium (NaOH) [39], Figure 8. These prepared derivatives can be suggested as building blocks of pharmaceuticals, thermosetting plastics, lubricants and unusual optical or electrical materials such as organic light-emitting diodes, solar cells and flat panel.





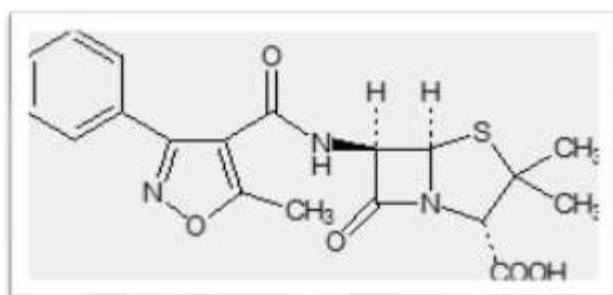
**Figure 8:** New fluorene – Isoxazoline derivatives starting from Claisen-Schmidt condensation.

New quinazolinone– isoxazoline hybrids were targeted compounds via 1,3-dipolar cycloaddition of aromatic nitrile oxides and quinazolinones with no effect of phenyl ring substituents through experimental and theoretical (Density Functional Theory (DFT)) studies [40], Figure 9. These studied can be with further investigation as new drug candidates in fungal, bacterial, tubercular, malarial and SARS-CoV-2 subjects.

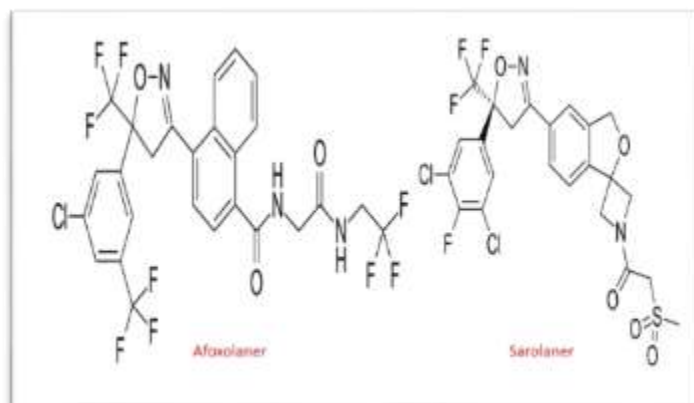


**Figure 9:** New quinazolinone– isoxazoline hybrids preparation pathways starting from anthanilic acid.

For human use, many isoxazolines were structural drug administrated for specific treatment such as Oxacillin that defines as semi-synthetic antibacterial related to penicillin (Figure 10). Clinical studies of available isoxazolines such as Afoxolaner, Sarolaner and others had been reported as veterinarian options like demodicosis treatment of dog and cat or other treatment with successful use after Food and Drug Administration (FDA) approval [41-43], Figure 11.



**Figure 10:** Oxacillin as semi-synthetic antibacterial related to penicillin contains isoxazolines moiety.



**Figure 11:** Isoxazoline derivatives for flea prevention and treatment.

## Conclusion

Isoxazoline derivatives are building blocks in organic synthesis for a number cyclic and acyclic heterocyclic materials can be obtained according to cyclization and rearrangement. Isoxazoline chemistry remains a unique model associated with various pharmacological activities. They represent a great interest to the research community for further development for safer and more effective therapeutics.

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