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## **Articles and Statements**

#### UDC 544

# A Review on a Highly Important Hetrocycle Quinazolinone Compounds and their Diverse Biological Activities

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#### Abstract

Quinazolinone and their derivatives have been studied extensively for various biological activities such as anti-inflammatory, antimicrobial, anticancer, anticonvulsant and anti-HIV activity etc. The purpose of this review was to collate literature work reported by researchers on quinazoline for their various pharmacological activities. Quinazolinone derivatives are one of the most active classes of compounds possessing a wide spectrum of biological activity. Recently several scientists have been reported that introduction of various heterocyclic moieties at quinazolinone nucleus modulate the activity. Various derivatives of quinazolinone have been synthesized and evaluated for their biological activities. This review might be helpful in the development of these novel lead molecules to potential drug candidates for future prospect.

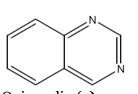
Keywords: Quinazoline, antimicrobial, Anti HIV, Anti cancer, biologically active.

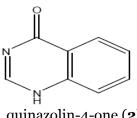
#### Introduction

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Quinazoline (1) are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological activities such as, antimicrobial, anti-cancer, anticonvulsant, anti-tubercular, etc [1-5]. Quinazolin is a heterocyclic compound consists of two fused six membered simple aromatic rings, a benzene ring and a pyrimidine ring. The quinazolin nucleus has attracted the attention of medicinal chemists due to its well known anticancer activity, and many substituted quinazolin derivatives have recently earned great interest in chemotherapy as antitumor drugs [6]. Pharmacologically quinazolin particularly quinazolin-4-one (2) or quinazolinone are the most important classes of heterocyclic compounds. Quinazolin-4-one is synthesized when the keto group is introduced in the pyrimidine ring of quinazolin. Quinazolinone compounds possess versatile biological activities; such as anticancer [7-8], antitubercular [9], antibacterial [10], antifungal [11], anti-HIV [12], anthelmintic [13], anti-inflammatory [14] antihypertensive activities [15] and also other activities.

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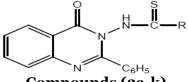
Quinazolin (1)

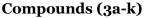
quinazolin-4-one (2)

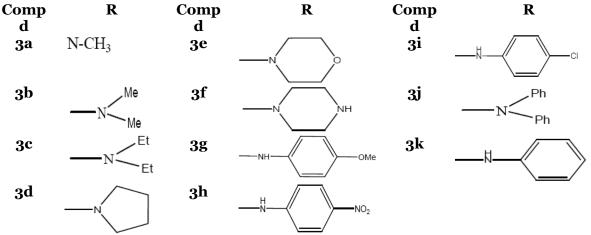
#### **Pharmacological activities**

The chemistry and pharmacology of quinazolinone have been of great importance to medicinal chemistry. Quinazolinones are versatile nitrogen containing heterocyclic compounds which are generally of little toxicity without side effects to human beings, and display a broad spectrum of biological activities like anticonvulsant and hypnotic [16], antimicrobial and antihistaminic [17], as well as antifungal activities [18].

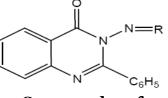
Analgesic and anti-inflammatory agents: Some quinazolin-4-one derivatives show promising analgesic and anti-inflammatory activities. The quinazoline derivatives might be beneficial in terms of biological activity for which further studies can be done to confirm it as a potential drug candidate. Some novel 2-phenyl-3-substituted quinazolin-4(3H) ones (3a-k) derivatives showed significant analgesic and anti-inflammatory activity compared with Diclofenac sodium as standard drug [19] compounds (3a-c) showed analgesic and anti-inflammatory acitivity and other compounds (3d-k) showed analgesic activity.







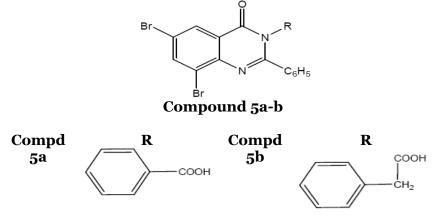
Quinazolinone fused Schiff bases (4) exhibited for anti-inflammatory activity [20].



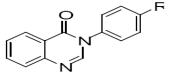
**Compound 4a-f** 

Compd	Substitution (R)	Compd	R	Compd	R
4a	2-nitrobenzaldehyde	4c	Acetaldehyde	4e	2-chlorobenzaldehyde
4b	Cinnamaldehyde	4d	Furfuraldehyde	4f	3-OCH <sub>3</sub> -4-OH-benzaldehyde

Quinazolin4-3(*H*)one compounds (5) showed analgesic and anti-inflammatory activity with varied potency when compared with the standard aspirin and indomethacin [22].

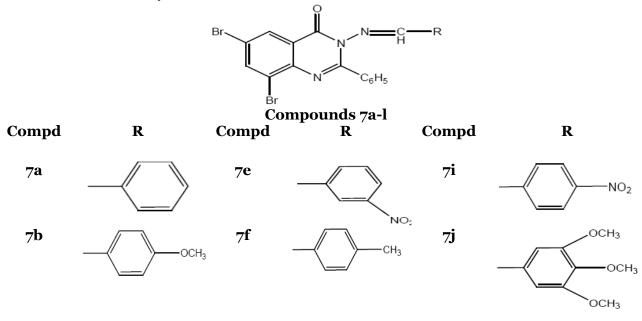


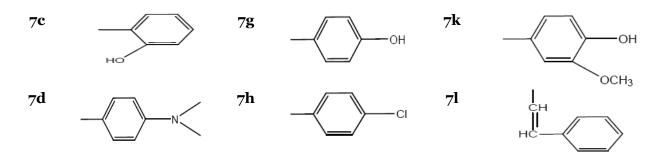
**Anti-microbial agents:** Anti-microbials cover large spectrum biological activities like anti bacterial, anti fungal, anti viral, anti leshmanial, antiprotozoal, antiplasmodial etc. Several derivatives of quinazolins possess potential anti-microbial activities. However, the substitution pattern in quinazolinone nucleus at 2/3 position by different aryl or heteroaryl moieties markedly modulates its antifungal and other biological activities. The 4-(3H)-quinazolinone derivative (**6**) from the reaction of anthranilic acid and primary aromatic amines with Vilsmeier reagent in a few minutes under microwave irradiation providing good yields. All the quinazolinone compounds were screened for their *In vitro* anti fungal activity against *Candida Albicans, Aspergilles Niger*. Some of these compounds showed good antifungal activity than reference drug [21].



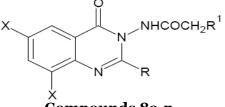
Compounds 6 ( $\mathbf{R}$ = CH<sub>3</sub>, Cl, NO<sub>2</sub>, Br, OCH<sub>3</sub>).

Some Schiff bases of 3-amino-6, 8-dibromo-2phenylquinazolin-4(3H)-ones (7a-l) and these compounds are screened as antimicrobial agents [22]. These compound were showed antifungal and antibacterial activity.





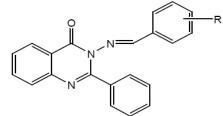
Some novel substituted 2-Imidazolyl-*N*-(4-oxoquinazolin-3(4*H*)-yl)-acetamides derivatives **(8a-p)** and evaluated the Antimicrobial activities [23].



**Compounds 8a-p** 

Compd	Χ	R	$\mathbf{R}_{1}$	Compd	Χ	R	$\mathbf{R}_{1}$
<b>8</b> a	Η	$C_6H_5$	Imidazolyl	<b>8i</b>	Br	$CH_3$	Imidazolyl
8b	Η	$C_6H_5$	2-Methyl Imidazolyl	<b>8</b> j	Br	$CH_3$	2-Methyl Imidazolyl
8c	Η	$C_6H_5$	2-Methyl benzi- imidazolyl	8k	Br	$\mathrm{CH}_3$	2-Methyl benzi- imidazolyl
8d	Η	$C_6H_5$	Benziimidazolyl	<b>8</b> l	Br	$CH_3$	Benziimidazolyl
8e 8f	Br Br	$\begin{array}{c} C_6H_5\\ C_6H_5 \end{array}$	Imidazolyl 2-Methyl Imidazolyl	8m 8n	Br Br	$\begin{array}{c} C_3H_7\\ C_3H_7 \end{array}$	Imidazolyl 2-Methyl Imidazolyl
8g	Br	$C_6H_5$	2-Methyl benzi- imidazolyl	80	Br	$C_3H_7$	2-Methyl benziimidazolyl
8h	Br	$C_6H_5$	Benziimidazolyl	<b>8</b> p	Br	$C_3H_7$	Benziimidazolyl

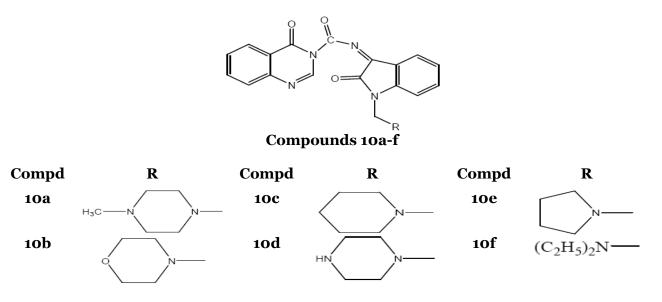
Some 3-(arylideneamino)-2-phenylquinazoline-4(3H)-ones derivatives **(9a-k)** exhibited antibacterial activity [24].



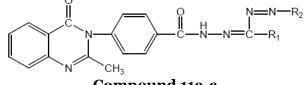
#### Compound 9-a-k

Compd	R	Compd	R	Compd	R	Compd	R
9a	2 –OH	9d	4 –N(CH <sub>3</sub> )	9g	4–OH	9j	$4 - NO_2$
9b	4 – OCH <sub>3</sub>	9e	4 –Cl	9h	4 – OCH <sub>3</sub>	9k	Н
9c	4 –F	9f	3 –OCH <sub>3</sub>	9i	4–OH		

Some quinazolin-4-(3H)-one clubbed isatin derivatives (**10a-f**) exhibited antibacterial and antifungal activity [25].



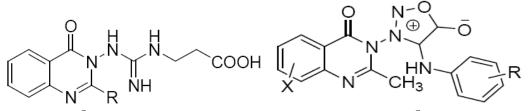
Several new quinazolinone formazans (11) which were evaluated for their antimicrobial, antifungal and antihelminthic property which were comparable to ciprofloxacin, fluconazole, albendazole and piperazine citrate respectively, some compounds were found to be potent [26].



Compound 11a-c

Compd	R1	$\mathbf{R}_{2}$	Compd	R <sub>1</sub>	$R_2$
11a 11b	$\begin{array}{l} C_6H_4NO_2\\ C_6H_4N(CH_3)_2\end{array}$	$C_6H_3FCl$ $C_6H_4Cl$	110	C <sub>6</sub> H <sub>3</sub> (OH)(OCH <sub>3</sub> )	C <sub>6</sub> H <sub>3</sub> FCl

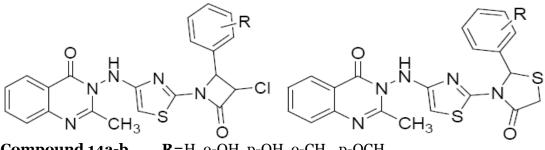
A series of 3-[3-(2-Substituted-4-oxo-4Hquinazolin-3-yl)-guanidino]-propionic acid derivatives (12) have been synthesied. Some compounds were more potent against *Monascus puppures, Aspergillus fumigates, A. parasiticus* and *Microsporum gypseum* than the reference drug Clotrimazole [27]. 2-methyl-3[sydnon-4-substitutedaniline-3'-yl] mono substituted quinazolin-4-(3H)-one (13) were synthesized. All the compounds and the reference drugs fluconazole and griseofulvin were evaluated for antifungal against different strains of fungi. *C. albicans, C. parapsilosis, A. fumigatus* and *A. niger* and showed equipotency towards *C. krusei* [28].



**Compound 12 R**= CH<sub>3</sub>, C<sub>6</sub>H<sub>5</sub>, 4-OCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>.

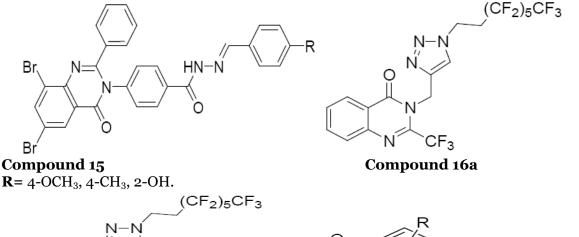
**Compound 13 X**= H, 6 Br; **R**= H, o-OCH3, p-OCH3, o-Cl, p-Cl

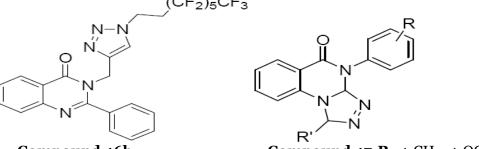
Compound 3-[2-(3-Chloro-2-oxo-4-Ar-azetidin-1-yl)-thiazol-4-ylamino]-2-methyl-3Hquinazolin-4-ones and 2-Methyl-3-(4'-oxo-2'-substutedphenyl-thiazolidin-3-ylamino)-3Hquinazolin-4-ones (**14**) were screened for their antifungal activity aganist *A. fumigates, A. niger, C. albicans* and *A. Flavus* [29].



**Compound 14a-b R**=H, o-OH, p-OH, o-CH<sub>3</sub>, p-OCH<sub>3</sub>.

Novel 6,8-dibromo-4(3H)quinazolinone derivatives (15) were found to exhibit the most potent *in vitro* anti-fungal activity [30]. A series of perfluoroalkyl-1H, 1,2,3- triazol-4-yl substituted quinazolines (**16a-b**) exhibited antimicrobial and antifungal activity were [31]. 4-(Substitutedphenyl)-1-(aryl)-3a,4-dihydro-1H-[1,2,4]triazolo[4,3-a]quinazolin-5-ones (17) have been tested for their antifungal activity aganist A. niger and phytophora. Interoduction of OCH<sub>3</sub>, OH and Cl groups to the hectrocyclic frame work enhence the antifungal activity [32].



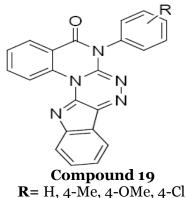


Compound 17 R=4-CH<sub>3</sub>, 4-OCH<sub>3</sub>, 4-Cl, 4-Br; R'= 4-**Compound 16b** OCH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 2- NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 2-ClC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 2-OHC<sub>6</sub>H<sub>4</sub>, 4-OHC<sub>6</sub>H<sub>4</sub>.

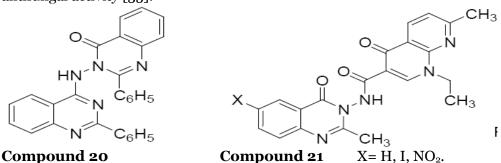
Anti-microbial studies of novel Schiff bases of 3-amino-6,8-dibromo-2-phenylquinazolin-4(3H)-ones (18) were described against the Gram positive, Gram-negative and fungi strains [33]. Quinazolinones (19) derivatives were screened for their antimicrobial activity against bacterial and fungal strain



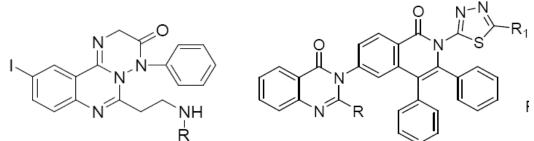
**Compound 18 R**= 4-OCH<sub>3</sub>, 2-OH, 4-OH, 4-Me, 4-Cl,4-NO<sub>2</sub>



A novel 2,3- substituted quinazolinon derivatives (20) were screened for their antifungal activity [34]. Quinazolone derivatives (21) of nalidixic acid showed potential antibacterial and antifungal activity [35].

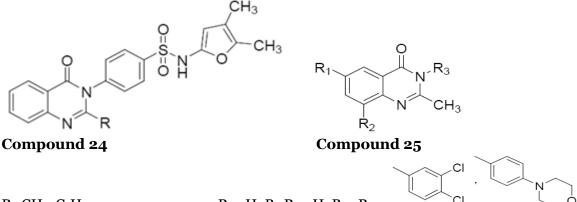


Some heterocyclic derivatives of quinazolinones (22) and (23) were assayed for their antifungal activitie. Some of these derivatives have shown good antifungal activity aganist fungal strain [37, 37].



**Compound 22** R= diff. Heterocycles. **Compound 23**  $R_1$  = diff. Aryl groups, R = H.

Antifungal activity exhibited by of some novel 6-bromo-2-methyl/phenyl-3-(sulphonamido) quinazolin-4(3H)-ones (**24**) were evaluated [38]. A series of 2-methylquinazolin- 4(3H)-ones (**25**) were exhibited antifungal activity [39].

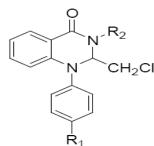


 $R=CH_3, C_6H_5$ 

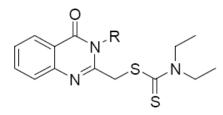
 $R_1 = H, Br R_2 = H, Br R_3 =$ 

Some new 1-substituted-2-(chloromethyl)-4-(1H)-quinazolinones (**26**) were synthesized and screened for their antifungal activity [40]. In-vitro antifungal activity aganist fungal strain and synthesis of some analogues of 2-methyl quinazolinones (**27**) were reported [41].

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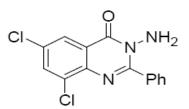


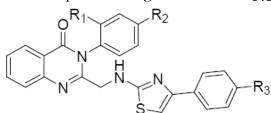
**Compound 26**  $R_1 = H$ , NO<sub>2</sub>, OCH<sub>3</sub>.  $R_2 =$  Substuted Ar



Compound 27  $R = H, 4 - CH_3C_6H_4, 4 - ClC_6H_4.$ 

Significant antifungal activity was observed for new 6,8-dichloro-2-phenyl-4-(3H)quinazolinone (28) compound [42]. A series of 3-aryl-2-(4´-arylthiazol-2´-yl aminomethyl)-quinazol in-4(3H)-ones (29) have been elicited for their impressive fungicidal activities [43].

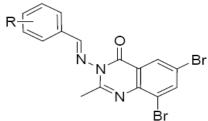


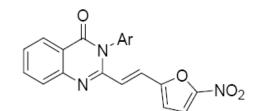


#### **Compound 28**

Compound 29  $R_1$ ,  $R_2$ ,  $R_3$ = H, Cl, OCH<sub>3</sub> etc

New 2,3- and 2,4-disubstituted quinazoline (30) derivatives showed potential antibacterial and antifungal activity [44]. 3-Aryl-2-[(5-nitro-2-furfuryl)vinyl]quinazolin-4-ones (31) were exhibited fungicidal activity [45].

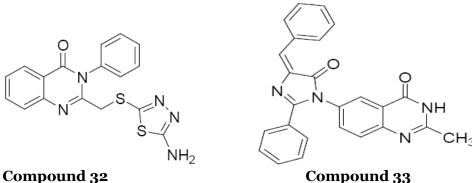




### **Compound 30**

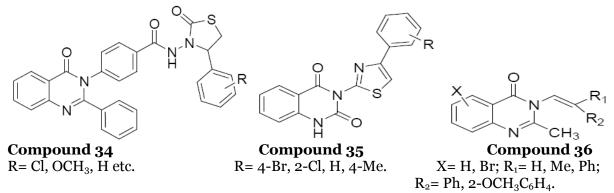
#### **Compound 31**

R= 2,4-Cl, 4-OH. Ar = Ph,  $4 - ClC_6H_4$ ,  $4 - CH_3C_6H_4$ ,  $3 - CH_3C_6H_4$ ,  $4 - OCH_3C_6H_4$ . Pharmacological screening of some quinazolinones (32) displayed activity against various Compound 6-(4 -substituted-benzylidene-2 -methyl fungal species /phenyl-5<sup>-</sup> [46]. imidazolinon-1 (-y)-2-methyl-4(3H)-quinazolinone (33) and assessed the compounds for their antifungal activity against A. niger [47].

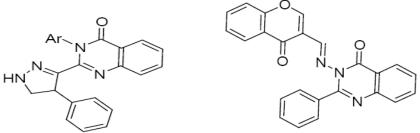


#### Compound 32

Potent antifungal activity in some newer quinazolinones (34) containing thiazolidinone moiety was reported [48]. 3-(4'-aryl-2'-thiazolyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazolinones (35) as promising antifungal agents [49]. Some Schiff bases of 3-amino-2-methylquinazolin-4(3H)-ones (**36**) were evaluated for their antifungal activity [50].



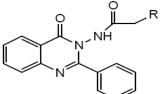
2-(4-aryl-2-pyrazolin-3-yl)-3-aryl-4(3H)-quinazolinones (**37**) have been prepared by cycloaddition of diazomethane. Some of these compounds have been found to exhibit good antifungal activity [51]. A condensation of four defferent 3-formylchromones with 2-methyl/phenyl-3-amino-4(3H)-quinazolinone and their dibromo analogs have been characterized as their respective 3-[N-(4-oxo-2-methyl/phenyl-3-quinazolinyl)-formimidoyl]-chromones (**38**). These compounds have been investigated as antifungal agent [52].



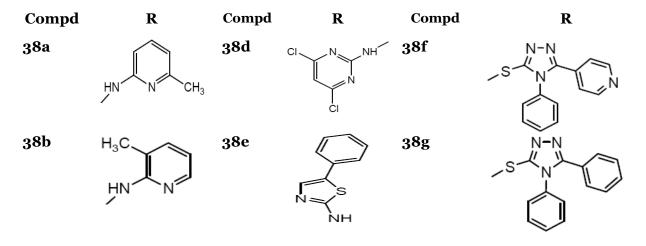
#### Compound 37

#### Compound 38

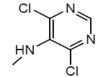
Antitubercular agents: There are no promising quinazolines marketed presently in the category of tuberculosis (TB). But several novel molecules have been synthesized in the past which showed promising results but unfortunately could not make it up to the marketing stage. Some 2-phenyl-3-substituted quinazolin-4(3*H*)-ones (**39a-g**) were exhibited anti-TB and antioxidant activities [53].



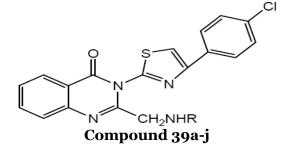
Compound 38a-g

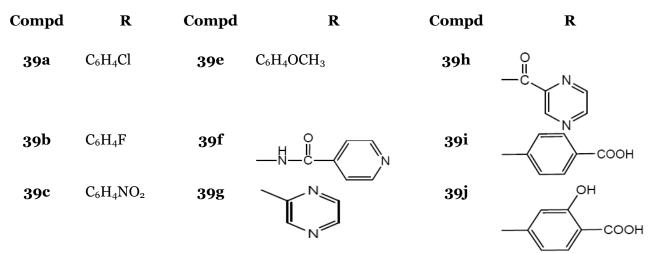


38c



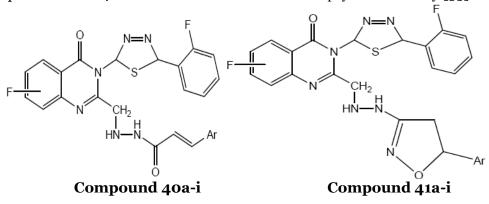
The N-3(4-(4-chlorophenyl thiazol-2-yl)-(2-(amino) methyl) quinazolin4(3H)-one **(39a-j**) and their derivative for anti-TB activity [54].



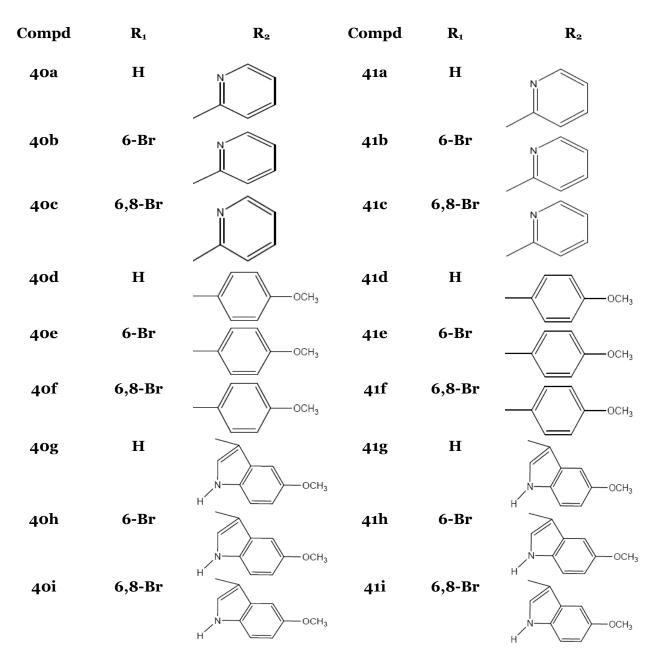


**39d** C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>

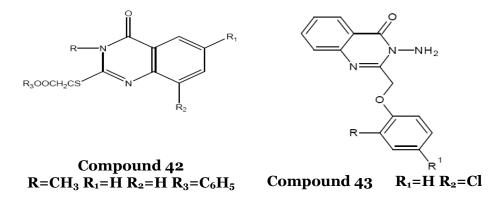
Anticonvulsant agents: Some quinazolinone derivatives showed promising anticonvulsant activities. For the future prospect quinazolinone can be the suitable candidate for the treatment of convulsions. Various thiadiazolylpyridinyl (**40a-i**) /indolylisoxazolyl (**41a-i**) quinazolinone-4-ones showed antconvulsant anti-psychotic activity [55].

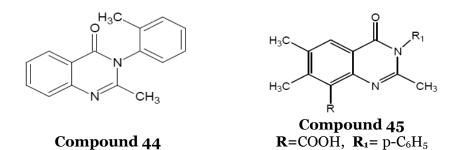


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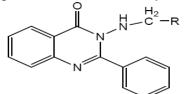


Some derivatives of 3H-quinazolin-4-one (42) through condensation reaction of their potassium salts with methyl, ethyl and phenyl isocyanate and synthesized compounds showed promising anticonvulsant activity [56]. Quinazolin-4-(3H)-one derivatives (43) were showed Anticonvulsant activity [57]. The 3,4-Dihydro-4-oxoquinazolin derivative (44,45) were exhibited anticonvulsant activity [58].

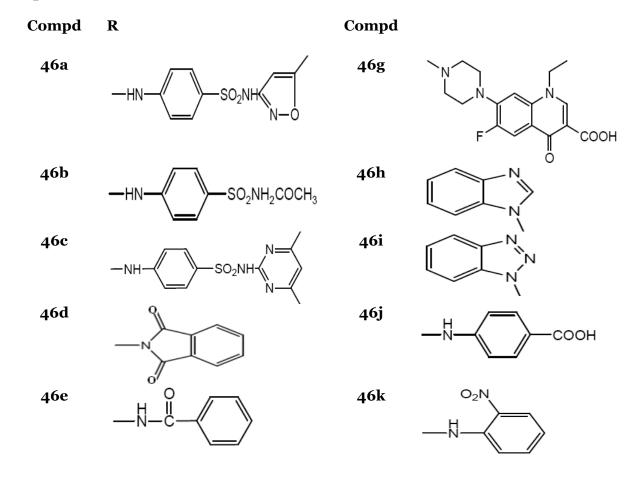


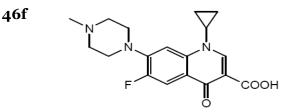


**Anti HIV agents:** Quinazolin-4-(3H)-one is a versatile lead molecule for the design of potential bioactive agents. The anti-HIV activity of 2-phenyl-3-substituted quinazolin-4-(3H)-ones. the 2-phenyl-3-substituted quinazolin-4-(3H)-ones [59-61]. A large number of quinazolines have been synthesized and studied for wide range of anti-viral activity. Some 2-phenyl 3-substituted quinazolin-4(3H)ones (**46**) were showed antiviral/ anti-HIV activity [62].

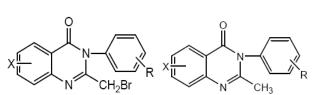


**Compounds 46a-k** 





**Antiparkinson agents:** Parkinsonism is caused due to deficiency of dopamine. After the attachment of dopamine with some quinazolin derivative shows promising antiparkinson activity. Series of 3-substituted phenyl 2-(3,4-dihydroxy phenyl ethyl amino)-6-substituted quinazolin-4-(3H) ones (47a-h, 48a-h and 49a-h) by the reaction of 3-Substituted phenyl -2-methylbromo-6-substituted quinazolin-4-(3H) ones with dopamine (3,4 dihydroxy phenyl ethyl amine) and has shown most potent antiparkinsonian activity [63]. 34



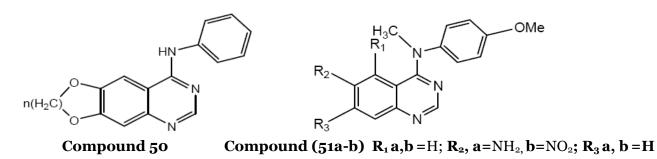
Compound 47a-h

Compound 48a-h

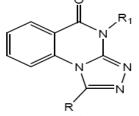
Сотроинd 49a-h

Compd	Х	R	Compd	X	R	Compd	X	R
47a	Н	H	48a	Н	H	49a	H	H
47b	Н	2-Cl	<b>48</b> b	Н	2-Cl	49b	H	2-Cl
47 <b>c</b>	Н	4-OCH <sub>3</sub> , 2-CH <sub>3</sub>	48c	Н	4-OCH <sub>3</sub> , 2-CH <sub>3</sub>	49c	H	4-OCH <sub>3</sub> , 2-CH <sub>3</sub>
<b>47d</b>	H	2-OCH <sub>3</sub>	48d	H	2-OCH <sub>3</sub>	49d	H	2-OCH <sub>3</sub>
<b>47e</b>	Br	Н	<b>48e</b>	Br	Н	<b>49e</b>	Br	Н
<b>47f</b>	Br	2-Cl	<b>48f</b>	Br	2-Cl	49f	Br	2-Cl
47g	Br	4-OCH <sub>3</sub> , 2-CH <sub>3</sub>	48g	Br	4-OCH <sub>3</sub> , 2-CH <sub>3</sub>	49g	Br Br	4-OCH <sub>3</sub> , 2-CH <sub>3</sub>
47h	Br	$2-OCH_3$	48h	Br	$2-OCH_3$	49h	Br	$2-OCH_3$

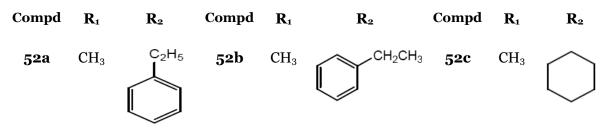
Anti cancer agents: Quinazolines occupy a promising section in the anti-cancer activity because of their specificity. There are so many researcher synthesize the quinazolin derivatives as anti cancer drug. Several dioxolane, dioxane (**50**), and dioxepine quinazoline derivatives and stated that size of the fused dioxygenated ring was crucial for the biological activity, the dioxane derivatives being the most promising class of this series. Derivatives were able to counteract EGF-induced EGFR phosphorylation and showed better or at least comparable potency with respect to PD153035 of which the following compound was promising [64]. Several N-methyl-4-(4-methoxyanilino) quinazolines (**51**) and stated that substitution at the 5-,6-,7-positions of the quinazoline and replacement of the quinazoline by other nitrogen-containing heterocycles. Replacement of the quinazoline ring with a quinoline, a benzo[d][1,2,3]triazine, or an isoquinoline ring showed that the nitrogen at the 1-position is important for activity, while the carbon at the 2-positioncan be replaced by a nitrogen and thenitrogen at the 3-position can be replaced by a carbon. The following compounds were found to be potent when compared with standard Azixa [65].



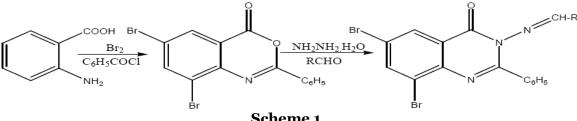
Anti-Histaminic agents: Some quinazoline possess good antihistaminic properties. Several 4-(3-ethylphenyl)-1-substituted-4H [1,2,4] triazolo [4,3-a] quinazolin-5-ones,4-(4ethylphenyl)-1-substituted-substituted-4*H* [1,2,4] triazolo [4, 3-a]quinazolin-5-ones and 1-substituted-4-cyclohexyl-4H-[1,2,4] triazolo [4,3-a] quinazolin-5-ones [66-68]. It was found that by varying substitution over the first position of the triazolo quinazoline (52) ring there was variation in the biological activity. The presence of methyl group showed better activity than the unsubstituted compound. With increased lipophilicity the activity remained but further increase in lipophilicity led to a decrease in activity. Replacement of the methyl group by other groups decreased the activity. The anti-histaminic potential was tested in vivo by comparing with Chlorpheniramine maleate in which the following compound showed promising anti histaminic activity with less sedation.



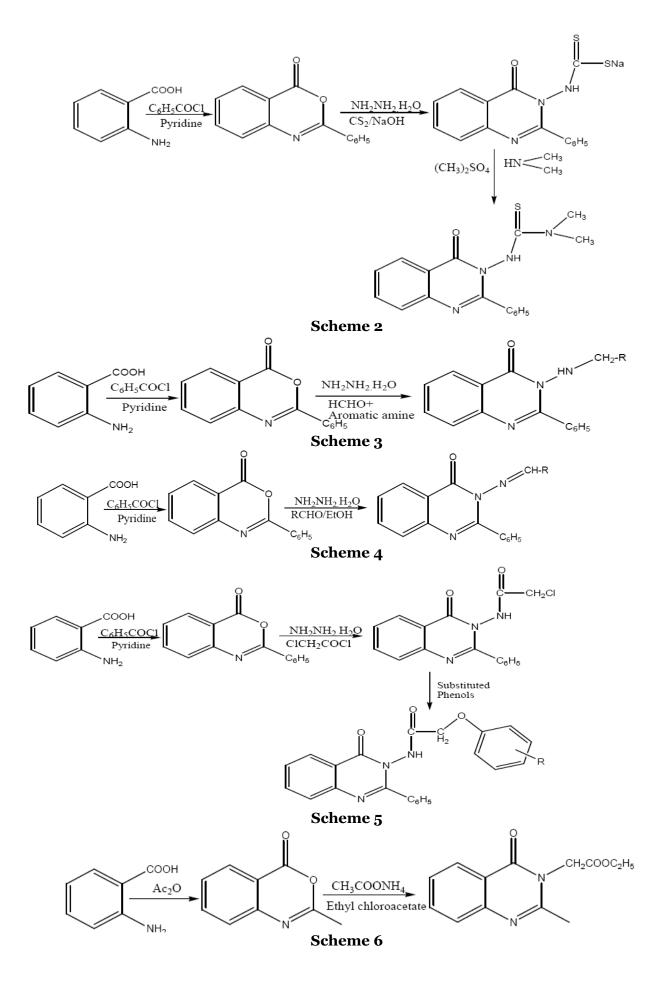
#### Compound 52



**Chemistry:** Various methods have been proposed by various researchers for the synthesis of quinazolin-4-ones as mentioned below. Anthranilic acid is the key reagent for the synthesis of quinazolin-4-ones. Some Schiff bases of 3-amino-6, 8-dibromo-2 phenylquinazolin-4(3H)-ones (Scheme 1) [69], some novel 2-phenyl-3-substituted quinazolin-4(3H)ones (Scheme 2) [70], some 2-phenyl 3-substituted quinazolin-4(3H)-ones derivatives (Scheme 3) [71], synthesized quinazolinone fused Schiff bases (Scheme 4) [72], synthesized novel quinazolinone derivatives (Scheme 5) [73] and synthesis of ethyl 2-(2-methyl-4-oxoquinazolin-3(4H)-yl) acetate as important analog and intermediate of 2,3 disubstituted quinazolinones (Scheme 6) [74].







#### Conclusion

Quinazolinone is a unique template that is associated with several biological activities. This article high lightened research work of many researchers reported in literature for different pharmacological activities on quinazolinone compounds synthesized. The review has presented comprehensive details of quinazolinone analogues, potent compounds reported for particular pharmacological activity and the method or technique involved in evaluation process. More investigations must be carried out to evaluate more activities of quinazolinone for many diseases whose treatment are difficult in the medical sciences. The literature reveals that the synthesized quinazoline compounds exhibited good biological activities. Several works found that substituted quinazolenone containing different heterosystems which were found to posses potent biological activities [75, 76]. By the present scenario it can be concluded that substituted quinazolenones have a great potential which remain to be disclosed till date.

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#### UDC 547

### Boric Acid Catalyzed Synthesis of 2-substituted Benzoxazoles in Aqueous Media

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#### Abstract

We report the synthesis of benzoxazoles using boric acid as catalyst in aqueous media. Synthesis of 2-substituted benzoxazoles derivatives from 2-amino phenol and a variety of aldehydes were developed under mild reaction conditions. The selection and use of water is emphasized as regards methods to minimize environmental impact. On completion of reaction the products were characterized by IR, NMR and Mass Spectra. These methods are more convenient and reactions can be carried out in higher yield.

Keywords: Benzoxazole, Aldehydes, 2-amino phenol, Boric acid, water.

#### Introduction

Five membered aromatic heterocyclic rings containing a C=N bond, such as benzoxazole is important structural units in natural products and in synthetic pharmaceutical and agrochemical compounds [1-2]. These compounds received a considerable amount of attention for their biological and therapeutic activities [3-4]. Therefore, the development of new methods for the synthesis of nitrogen containing heterocycles is still a focus of intense and containing interest in the organic chemistry as well as in pharmaceutical and agrochemical chemistry. Benzoxazole is an aromatic organic compound with a molecular formula  $C_7H_5NO$ , a benzene fused oxazole ring structure and an odour similar to pyridine. Molecules with benzoxazole moieties are attractive targets for synthesis since they often exhibit diverse and important biological activities such as antibiotic [5], antifungal [6], antiviral [7], anticancer [8], antimicrobial [9], and antiparkinson [10] properties. They have also been used as ligands for asymmetric transformations [11].

A variety of oxidants and catalysts have been used for preparation of benzoxazoles. Different catalysts and different methods were also reported for the synthesis of these heterocycles like  $Pd(OAc)_2$  [12],  $ZrOCl_2 \otimes H_2O$  [13], silica sulfuric acid [14], silica supported sodium hydrogen sulfate [15], Indian 190 resin [16], ([Hbim]BF<sub>4</sub>) [17], methane sulphonic acid [18],  $Cu(OTf)_2$  [19], copper (II) oxide nanoparticles [20], PCC-supported silica gel [21],  $In(OTf)_3$  [22],  $SnCl_2$  [23], DDQ [24],  $BF_3 \cdot OEt_2$  [25],  $Mn(OAc)_3$  [26],  $PhI(OAc)_2$  [27],  $Th^+ClO_4^-$  [28],  $BaMnO_4$  [29],  $NiO_2$  [30] and  $Pb(OAc)_4$  [31].

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Although these methods worked nicely in many cases, however, some of these suffer from one or more limitations such as low yields, use of volatile or toxic organic solvents, requirement of excess amounts of catalysts or reagents, special apparatus and harsh reaction conditions. Consequently, development of convenient, high yield and environmentally benign procedure for synthesis of benzoxazoles is still a challenging research. Due to the important biological activity of benzoxazoles and in line with our research works in synthesis of this ring system, we wish to report a simple procedure for preparation of 2-aryl benzoxazoles through a condensation reaction of 2-amino phenol and aromatic aldehydes in the presence of boric acid as catalyst in aqueous media.

#### **Experimental section**

Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. Solvents were dried using standard methods and distilled before use. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker AM-400 MHz instruments in CDCl<sub>3</sub> with TMS as internal standard. The chemical shifts ( $\delta$ ) are reported in ppm and coupling constants (J) in Hz. Chemical shifts are reported in parts per million ( $\delta$ ) relative to CDCl<sub>3</sub> (7.27 ppm) for <sup>1</sup>H NMR data and CDCl<sub>3</sub> (77.0 ppm) for <sup>13</sup>C NMR data. Multiplicities are indicated: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), dd (double doublets), m (multiplet). Column chromatography was performed with silica gel (200-300 meshes). Thin layer chromatography (TLC) was visualized using UV light.

#### General procedure for the synthesis of benzoxazoles (3a-j)

A mixture of 2-amino phenol (1.0 mmol) and aldehyde (1.2 mmol) in the presence of and boric acid (10 mol %) in water (5 mL) was stirred at room temperature for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried over  $Na_2SO_4$  and concentrated under reduced pressure. The crude products were purified by column chromatography. All the products were identified by spectral (IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass) and analytical data. The synthetic route was depicted in scheme I.

#### Spectral data for selected compounds:

**2-phenylbenzo[d]oxazole (3a):** yield 90%, white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.29-8.27 (m, 2H), 7.82-7.78 (m, 1H), 7.62-7.58 (m, 1H), 7.56-7.53 (m, 3H), 7.39-7.35 (m, 2H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  163.0, 150.7, 142.0, 131.5, 128.9, 127.6, 127.1, 125.1, 124.6, 120.0, 110.6 ppm.

**2-(p-tolyl)benzo[d]oxazole (3b):** yield 71%, white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.16 (d, J = 8.4 Hz, 2H), 7.78-7.76 (m, 1H), 7.59-7.57 (m, 1H), 7.36-7.33 (m, 4H), 2.45 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  163.3, 150.7, 142.1, 129.6, 127.6, 124.9, 124.5, 124.3, 119.8, 110.5, 21.7 ppm.

**2-(4-methoxyphenyl)benzo[d]oxazole (3c):** yield 96%, white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.21 (d, J = 8.8 Hz, 2H), 7.76-7.73 (m, 1H), 7.57-7.55 (m, 1H), 7.36-7.30 (m, 2H), 7.03 (d, J = 8.4 Hz, 2H), 3.90 (s, 3H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  163.1, 162.3, 150.6, 142.2, 129.3, 124.6, 124.4, 119.7, 119.6, 114.3, 110.3, 55.4 ppm.

**2-(4-chlorophenyl)benzo[d]oxazole (3d):** yield 94%, white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.20 (d, J = 8.4 Hz, 2H), 7.79-7.76 (m, 1H), 7.60-7.58 (m, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.40-7.36 (m, 2H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  162.1, 150.8, 142.1, 137.8, 129.3, 128.9, 125.7, 125.4, 124.8, 120.2, 110 ppm.

**2-(3-chlorophenyl)benzo[d]oxazole (3e):** yield 93%, white solid. <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta$  8.26 (d, J = 2.0 Hz, 1H), 8.16-8.13 (m, 1H), 7.81-7.77 (m, 1H), 7.62-7.57 (m, 1H), 7.52-

7.50 (d, J = 8.4 Hz, 2H), 7.40-7.36 (m, 2H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  161.6, 150.7, 141.9, 135.0, 131.5, 130.2, 128.8, 127.6, 125.6, 125.5, 124.8, 120.2, 110.7 ppm.

**2-(4-fluorophenyl)benzo[d]oxazole (3f):** yield 75%, white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.30-8.25 (m, 2H), 7.80-7.76 (m, 1H), 7.60-7.57 (m, 1H), 7.39-7.35 (m, 2H), 7.25-7.20 (m, 2H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  166.1, 163.5, 162.1, 150.7, 142.0, 129.9 (d, *J* = 9.0 Hz), 125.1, 124.7, 123.5 (d, *J* = 3.0 Hz), 120.0, 116.2 (d, *J* = 22.0 Hz), 110.6 ppm.

**2-(4-bromophenyl)benzo[d]oxazole (3g):** yield 84%, white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.12 (d, J = 7.2 Hz, 2H), 7.80-7.75 (m, 1H), 7.66 (d, J = 8.8 Hz, 2H), 7.60-7.56 (m, 1H), 7.39-7.35 (m, 2H). ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  162.1, 150.7, 142.0, 132.2, 129.0, 128.9, 126.2, 126.1, 125.4, 125.1, 124.7, 120.1, 120.0, 110.6 ppm.

**2-(4-(trifluoromethyl)phenyl)benzo[d]oxazole (3h):** yield 82%, white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.39 (d, *J* = 8.0 Hz, 2H), 7.84-7.79 (m, 3H), 7.64-7.60 (m, 1H), 7.44-7.38 (m, 2H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 161.5, 150.8, 141.9, 133.1, 132.8, 130.4, 127.8, 126.0, 125.9, 125.9, 125.8, 125.1, 124.9, 122.4, 120.4, 110.8 ppm.

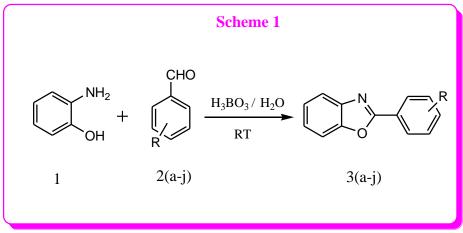
**4-(benzo[d]oxazol-2-yl)benzonitrile (3i):** yield 79%, white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.38 (d, J = 8.8 Hz, 2H), 7.85-7.82 (m, 3H), 7.65-7.62 (m, 1H), 7.46-7.40 (m, 2H).ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  160.9, 150.9, 141.8, 132.7, 131.1, 127.9, 126.2, 125.1, 120.6, 118.2, 114.7, 110.9 ppm.

**2-(2,4,6-trimethylphenyl)benzo[d]oxazole (3j):** yield 67%, white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.85-7.83 (m, 1H), 7.61-7.59 (m, 1H), 7.42-7.39 (m, 2H), 6.99 (m, 2H), 2.37 (m, 3H), 2.30 (s, 6H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 163.3, 150.6, 141.5, 140.3, 138.4, 128.6, 124.9, 124.2, 120.1, 110.6, 21.3, 20.3 ppm.

#### **Results and discussions**

In continuation of our research work using boric acid in organic synthesis here we are pleased to report that amixture of aldehyde, 2-amino phenol in the presence of boric acid (10mol%) in H<sub>2</sub>O at room temperature furnished benzoxazoles in good yields (Scheme 1). We chose the reaction between 2-amino phenol and benzaldehyde as the model reaction. First we carried out model reaction in the presence of a catalyst (Table 1, entry 1) and found that the reaction proceed. By using these optimized conditions, various benzoxazole derivatives **3a-j** were synthesized in shorter time as well as in high yields using boric acid as the catalyst. A wide range of aromatic and heteroaryl aldehydes were subjected to prove the general applicability of our present procedure which is summarized in Table 1. It was observed that the aromatic aldehyde bearing an electron donating substituent (Table 1). We have synthesized compounds **3a-j** bearing an electron donating substituent (Table 1). We have synthesized compounds **3a, 3h, 3g, 3h, & 3i** bearing an electron withdrawing substituent ( $-\text{OCH}_3$ ) **3c** with high yields were as compounds **3f, 3g, 3h, & 3i** bearing an electron withdrawing substituent (-F, -Br,  $CF_3$ , -CN). The reactions are clean and highly selective affording exclusively benzoxazoles in high yields in a short reaction time.

Reactions at different conditions in the presence of boric acid revealed that the best conditions were using water as solvent at room temperature. After completion of the reaction, the catalyst (boric acid) can easily be separated from the reaction mixture by washing the product with water.



**Scheme I:** The synthetic route

In our preliminarily investigation on the model reaction of 2-amino phenol and benzaldehyde, it was found that the reaction could be finished under very simple reaction conditions in the presence of boric acid as catalyst in aqueous media which gives the desired benzoxazole product in good yield (Table 1).

Entry	Aldehyde	Product	Yield (%)
1	()-сно		90
2	н₃с-√сно		71
3	н₃со-√у-сно		96
4	сі————————————————————————————————————		94
5	СІ		93
6	Г-√СНО	F	75
7	Br — СНО	Br	84
8	F₃C-⟨)−СНО	$\square \square $	82

9	NC- СНО	79
10	- Сно	67

The main features of our new reaction are as follows:

(1) The simplicity of the system;

(2) The condensation reaction could be performed exclusively using cheap, commercially available chemicals;

(3) Easy separation of products from the reaction mixture;

(4) The method is cost-effective and environmentally benign.

#### Conclusion

In conclusion, we have demonstrated that 2-substituted benzoxazoles can be synthesized from 2-aminophenols and aldehydes in the presence of boric acid as catalyst in aqueous media in good yields. The present boric acid as catalyst in aqueous media reaction is an alternative route to benzoxazole synthesis using 2-aminophenols and aldehydes.

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### Thermal Activation of Iodine-Containing PbSe thin Films

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#### Abstract

Influence of iodine addition on elemental composition, structure and surface morphology on lead selenide thin films prepared by chemical bath deposition method was studied by methods of X-ray diffraction analysis and scanning electron microscopy with elemental energy-dispersive analysis. Content of iodine in thin films raised to 4.25 at.% with increasing concentration of ammonium iodide in bath solution. Influence of anneal on structure and crystallite size of lead selenide thin films was found.

**Keywords:** chemical bath deposition, thin films, lead selenide, iodine doping, annealing, thermal activation, X-ray diffraction, scanning electron microscopy, doping, semiconductors

#### Introduction

Thin films based on lead chalcogenide are one of the most promising semiconductor material. Lead chalcogenides have high photovoltaic properties in spectral range from 2.0 to 5.0 micrometer, due to they have been found wide applications in photodetector [1].

Both physical and chemical methods of deposition have been used for prepare lead chalcogenide. Thermal evaporation technique [1-4] and chemical bath deposition [1, 5-7] are the most popular method which permit to obtain polycrystalline materials providing a different structure and physical properties. The chemical bath deposition method is low-cost processes and the films are of comparable quality to those obtained by more complicated and expensive physical deposition processes. It can be used for preparation of high-quality lead chalcogenide films with control of the deposition parameters such as stirring period, reaction time, bath temperature, solution pH, and added impurities.

As-deposited thin films also don't have photosensitivity because they are subject to hightemperature annealing in an oxygen atmosphere. Changing the conditions of thermal activation, it can also affect the photovoltaic properties of materials [8]. Alloy addition may occur both during the synthesis of the films and during annealing. Iodine-containing additions use in the chemical deposition of thin films because the iodine provides with high sensitive to IR radiation [2, 3, 5, 6].

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It was found that iodine stimulates physical-chemical processes conductive improvement of photosensitivity.

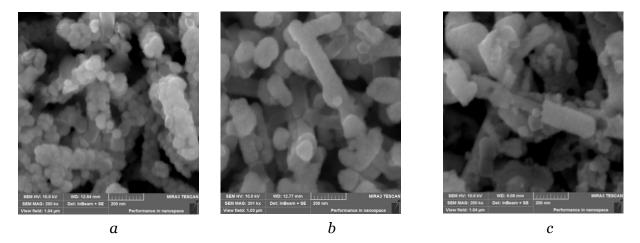
In the present study we investigated thermal activation of iodine-containing PbSe thin films on composition, morphology and structure.

#### Materials and methods

PeSe thin films were prepared by means of chemical bath deposition technique. The glassceramics substrate were previously cleaned. Bath solution contained lead acetate Pb(CH<sub>3</sub>COO)<sub>2</sub>, selenourea CSe(NH<sub>2</sub>)<sub>2</sub>, ammonium hydroxide NH<sub>4</sub>OH, and ammonium iodine NH<sub>4</sub>I as s dopant. The reaction temperature was fixed 353 K. The films were annealed at 513-548 K. The film thickness was measured by means of interference microscopy on microinterferometer Linnika MII-4M. The surface morphology and elemental composition of films were characterized by scanning electron microscopy with elemental energy-dispersive analysis (EDX) using SEM JEOL JSM–5900LV. The structure of the films was analyzed by X-ray diffraction using DRON-UM1 using Cu Kα radiation. X-ray diffraction patterns were recorded in the range 20 from 20 to 75°.

#### Discussion

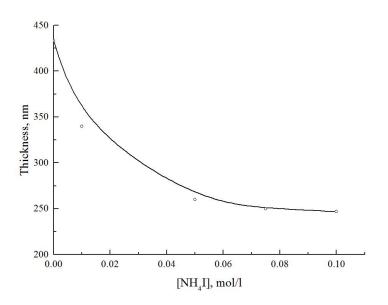
The SEM images of as-deposited PbSe thin films prepared by chemical bath deposition are shown in Fig. 1.

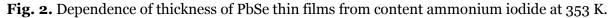


**Fig. 1.** SEM images of as-deposited undoped PbSe thin films (a) and doped PbSe(I) prepared from solution containing NH<sub>4</sub>I mol/L: 0.05 (b); 0.20 (c).

As shown in Fig. 1 PbSe thin films are not compact. Their crystallite are randomly arranged on the surface. The crystallite size of undoped films (Fig. 1a) is about 1 mkm in length and it consists of nanoparticles with average size 42 nm. The structure of films is disordered. The crystalline particles of films prepared from solution with concentration of  $NH_4I$  0.05 mol/l (Fig. 1b) are degraded and decreased to 0.5 mkm. The polygonized crystal of films is almost destroyed by addition on bath 0.20 mol/l of  $NH_4I$  (Fig. 1c). The average size of nanoparticles decreases to 23 nm. The crystallite size decreases due to spontaneous formation a large number of nucleation center [5]. Therefore synthesis in the early stages of grow represents bulk crystallization. Iodine is sorbed on crystal face and blocks crystal grow. Injection of ammonium iodine in bath solution changes not only morphology thin films but also thickness of forming layer.

Dependence of thickness of lead selenide thin films from concentration of ammonium iodide is shown in Fig. 2. Thickness of PbSe films decreases twice with increasing of content of  $NH_4I$  to 0.20 mol/l by comparison with undoped samples. This could be due to decreasing of content of lead in reacting system by formation of complex with I-ions and PbOHI slightly soluble subsalt [3].

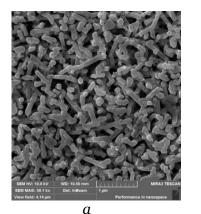


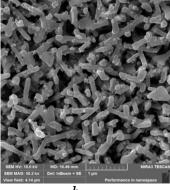


Stoichiometry of undoped and doped PbSe films was found by elemental energy-dispersive analysis. The ratio of lead and selenium is 1:1 at undoped films. Content of iodine in films monotonic increases to 4.25 at % with increasing of ammonium iodine in bath solution to 0.20 mol/l and content of selenium decreases. This occurs because iodine enters into the composition as insoluble  $PbI_2$ .

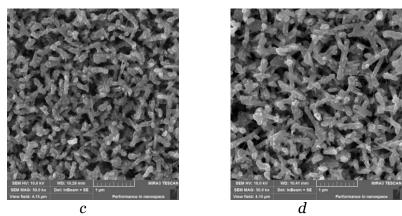
The annealing of lead selenide thin films was carried out in quasi-closed volume air. Preliminary experiments have shown that we have obtained samples do not withstand temperatures above 573 K. Therefore, thermal sensitization films of lead selenide were carried out in a temperature range of 503-548 K.

Fig. 3 demonstrates the SEM images of annealing films of PbSe. The surface of PbSe was transformed in more defect structure. Increase annealing temperature result in more damage surface. The film, which was synthesized from a less concentrated on the dopant in solution, is more uniform and evenly distributed over substrate. The crystallite length of annealing films decreases to 0.5 mkm (Fig. 3c) and 0.7 mkm (Fig. 3d).





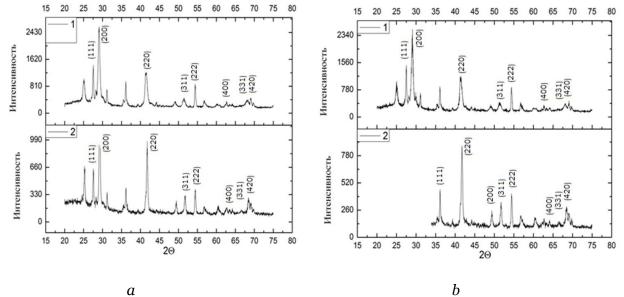
b



**Fig. 3.** SEM images of annealing PbSe thin films prepared from solution containing NH<sub>4</sub>I mol/L: 0.05 (a, b); 0.20 (c, d). Temperature of thermoactivation: 513 K (a, c) and 538 K (b, d).

The XRD patterns of as-deposited and annealing PbSe thin films are shown in Fig. 4. The reflection peaks of PbSe phase were observed for all samples that is to say all films are onephase. The peaks of XRD patterns of PbSe correspond to cubic lattice NaCl (B1, Fm-3m) in accordance with the standard card PDF Card No. 03-065-0133. The peaks of glassceramics substrate were observed (PDF Card No. 01-071-4513). Another phase are not observed. Annealing samples are more crystalline then as-deposited films.

The introduction of iodine in the film does not lead to a drastic change in the preferred orientation of micro-crystallites PbSe. Growth of crystallites along [200] direction is predominant iodine-doped films. At the same time the preferred growth orientation in the iodine-doped PbSe films changed to [220] with increasing of content of iodine. Change of texture is concerned with saturation of PbSe film by iodine prevented the growth along [200] direction, and the maximum concentration of ammonium iodine leads to destruction of polygonized crystal.



**Fig. 4.** XRD pattern of annealing PbSe thin films at 513 K (1) and as-deposited films (2). Content of  $NH_4I$  in reactor mixture is: 0.05 M (a) and 0.2 M (b).

#### Conclusion

We have successfully deposited PbSe thin films by using the CBD method. Addition of ammonium iodide in bath solution for chemical bath deposition of PbSe thin films influence deeply on their thickness and microstructure. Thermal sensitization of lead selenide films was carried out at 503-548 K. Annealing films have more uniform surface then as-deposited. Increase of

concentration of ammonium iodide in bath solution to 0.20 mol/L lead to gradual variation preferred orientation of PbSe from [200] to [220].

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