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A review on some synthetic methods of 4(3*H*)-quinazolinone and benzotriazepine derivatives and their biological activities

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Abstract: This concise review provides an overview of some synthetic methods utilized for the preparation of 4(3*H*)-quinazolinone and benzotriazepine derivatives, and explores their diverse biological activities. The review highlights the significance of these compounds in medicinal chemistry and discusses selected synthetic approaches employed in their synthesis. Additionally, it examines the range of biological activities exhibited by these derivatives and briefly discusses their potential applications. This succinct review serves as a valuable resource for researchers interested in the synthesis and biological evaluation of 4(3*H*)-quinazolinone and benzotriazepine derivatives.

Keywords: Synthesis; heterocyclic compounds; 4(3*H*)-quinazolinone; benzotriazepine; biological activities; medicinal chemistry.

1. Introduction

Heterocyclic compounds are cyclic organic compounds having at least one atom other than carbon such as N, O, or S, ... (hetero-atoms), in their rings. These compounds play a vital role in various fields, including agriculture and medicinal chemistry, due to their diverse chemical properties and biological activities[1-10]. In agriculture, heterocyclic compounds have been extensively utilized as active ingredients and exhibit potent insecticidal, fungicidal, and herbicidal properties, making them essential tools in modern agricultural practices[11-14].The relationship between agriculture and chemistry is deeply intertwined, since chemistry playing a pivotal role in advancing agricultural practices and addressing the challenges facing modern farming[15-18]. The importance of heterocyclic compounds in medicinal chemistry extends beyond their direct use as drugs[19-20].

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Synthesis and biological activities of 4(3H)-quinazolinone and benzotriazepine derivatives

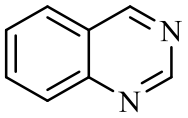
4(3*H*)-quinazolinone and benzotriazepine derivatives are two important classes of heterocyclic compounds that have attracted significant attention in the field of medicinal chemistry. These compounds exhibit diverse biological activities and have shown promising potential as therapeutic agents in various disease fields and a novel series of 2,3-dihydroquinazolin-4(1*H*)-one and benzotriazepin-5(2*H*)-one derivatives could be obtained by starting from the same intermediate according to varying the substituent on the benzamide moiety of the key intermediate or the conditions of the reactions utilized in this syntheses[21-24]. The 4(3*H*)-quinazolinone scaffold is a bicyclic heterocycle consisting of a quinazoline ring bearing a carbonyl group at the 4-position. This structural motif has been widely explored in drug discovery due to its versatile pharmacological properties. Quinazolinone derivatives have been reported to possess a wide range of biological activities, including anticancer, antimicrobial, anti-inflammatory, and antiviral properties[25-28]. Such diverse activities have made quinazolinones attractive targets for the development of new therapeutic agents.

On the other hand, benzotriazepines are another class of heterocyclic compounds that exhibit a bicyclic structure composed of a benzene ring fused with a triazepine ring. Benzotriazepine derivatives have shown significant potential as central nervous system (CNS) modulators[29-30]. The structural diversity and pharmacological potential of both 4(3*H*)-quinazolinone and benzotriazepine derivatives have attracted the interest of medicinal chemists and pharmaceutical researchers. Extensive efforts have been made to design and synthesize novel compounds within these scaffolds, aiming to enhance their therapeutic properties, selectivity, and safety profiles.

2. Chemistry

2.1. Chemistry of 4(3H)-quinazolinone Derivatives

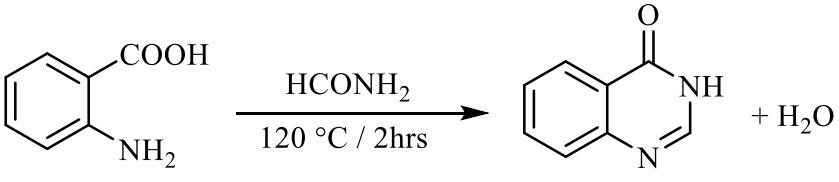
Of the many derivatives of quinazoline system (**1**) known so far, ketoquinazolines or quinazolinones, are the most important ones. Depending upon the position of the keto or oxo group, these compounds may be classified into two types: 2(1*H*)-quinazolinones or 1,2-dihydro-2-oxoquinazolines and 4(3*H*)-quinazolinones or 3,4-dihydro-4-oxoquinazolines (Figure 1)[31].



1

Figure 1. The quinazoline system

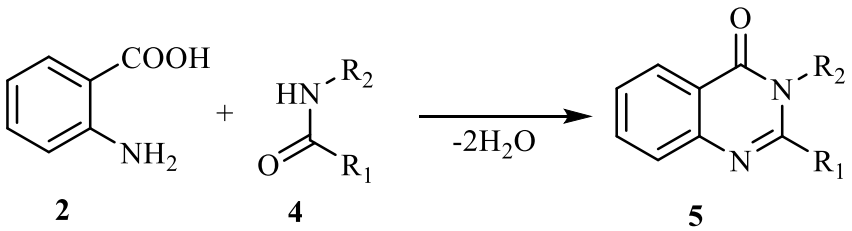
In general, the quinazolinone skeleton is simply built up from anthranilic acid or one of its derivatives. The most common synthesis of 4(3*H*)-quinazolinone is through a reaction which was first described by Niementowski[32] in 1895 where the anthranilic acid (**2**) was heated in an open container with excess formamide at 120°C to give 4(3*H*)-quinazolinone (**3**) (Figure 2).



2 **3**

Figure 2. Synthesis of quinazolinone skeleton

There action was modified to use a variety of substituted amides (**4**) instead of formamide as starting material to give the corresponding substituted 4(3*H*)-quinazolinones (**5**) according to the following Niementowski[32] quinazolinones synthesis (Figure 3).



2 **4** **5**

R_1, R_2 = CH_3, C_2H_5, C_3H_7.

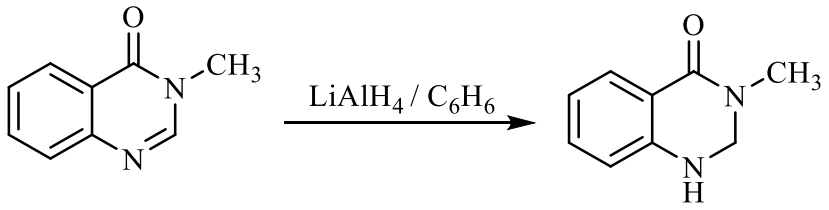
Figure 3. Synthesis of compound **5**

Anthranilic acid esters or anthranilamides were utilized to synthesize the target 4(3*H*)-quinazolinone derivatives instead of anthranilic acid itself.[33-35] Moreover, 4(3*H*)-quinazolinones were also synthesized starting from *o*-disubstituted benzene derivatives such as 2-aminobenzonitrile, 2-fluoro-substituted benzoyl chlorides, 2-nitrobenzoic acid and 2,6-difluoro-4- methoxybenzoic acid.[36-39] Other methods using isatoic anhydrides, isatin, 4,1-benzoxazepine-2,5(1*H*,3*H*)-diones or 3-arylideneamino-1,2,3-benzotriazin-4-ones were also developed for the synthesis of 4(3*H*)-quinazolinones[40-43].

The present part describes different methods for the preparation of partially saturated derivatives of 4(3*H*)-quinazolinones namely dihydroquinazolinone starting from the following:

(A) <u>Reduction of 4(3H)-Quinazolinones</u>

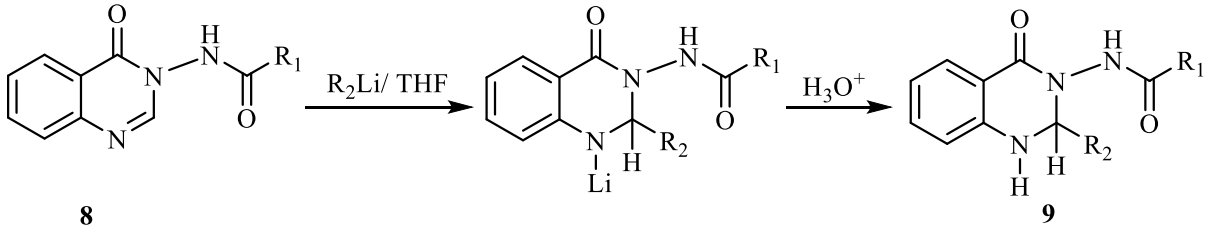
2,3-Dihydro-3-methyl-4(1*H*)-quinazolinone (**7**) was prepared through reduction of 3-methyl-4(3*H*)-quinazolinone (**6**) using lithium aluminium hydride ($LiAlH_4$) in benzene (Figure 4) [44].



6 **7**

Figure 4. Synthesis of compound **7**

In addition, reduction of 3-(pivaloylamino)- and 3-(acetylamino)-4(3*H*)-quinazolinones (**8**) was achieved using alkyl lithium reagents whereas nucleophilic attack at the imine bond occurred, giving the corresponding 1,2- addition products (**9**) (Figure 5)[45].



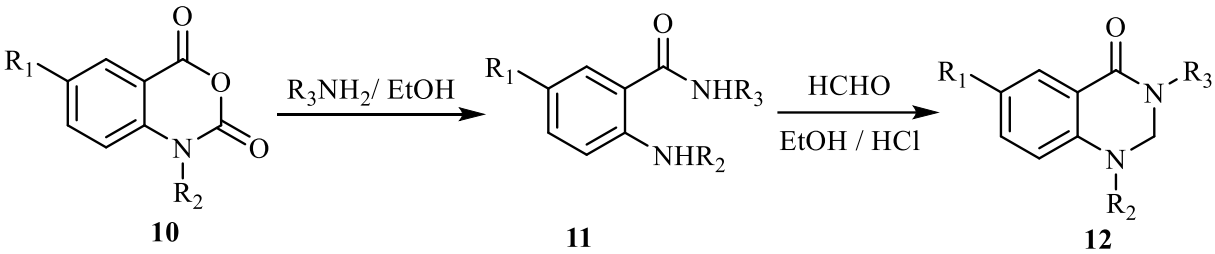
8 **9**

R_1= *t*-Bu, CH_3. R_2= n-Bu, *t*-Bu, CH_3.

Figure 5. Synthesis of compound **9** derivatives

(B) Isatoic Anhydrides

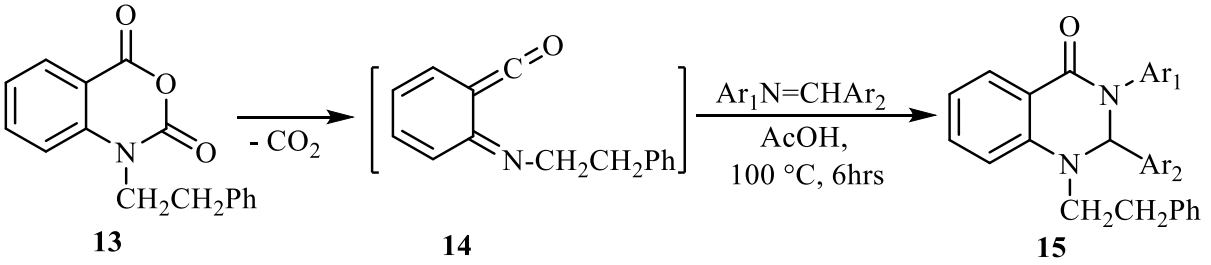
The reaction of the isatoic anhydrides (**10**) with different amines in ethanol afforded the amide intermediates (**11**) which were cyclized in acidic condition in the presence of formaldehyde to give the desired 1,2-dihydro-4(3*H*)-quinazolinone derivatives (**12**) (Figure 6)[46].



R_1= Br, 4-Br-2-$FC_6H_3CH_2$, CH_3OCOCH_2;
R_2,R_3= *t*-$BuOCOCH_2$, 3,4-$Cl_2C_6H_3CH_2$, H, $EtOCOCH_2$, 4-$CH_3OC_6H_4CH_2$.

Figure 6. Synthesis of compound **12** derivatives

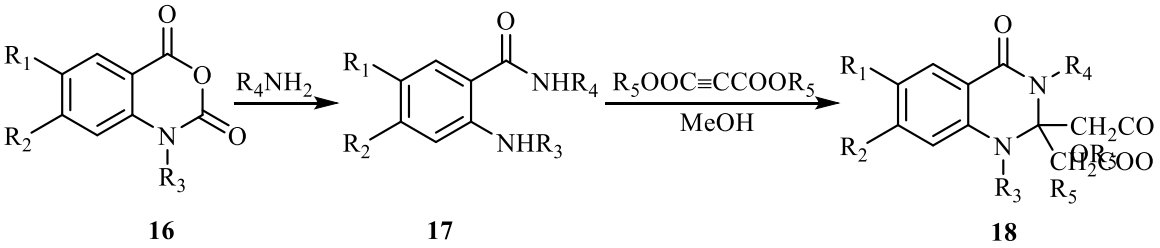
Moreover, the dihydroquinazolinones (**15**) were obtained via [4+2] cycloaddition of the decarboxylated intermediate (**14**) of isatoic anhydride (**13**) with different azomethines (Figure 7)[46].



Ar_1, Ar_2= Different Aromatic Rings.

Figure 7. Synthesis of compound **15** derivatives

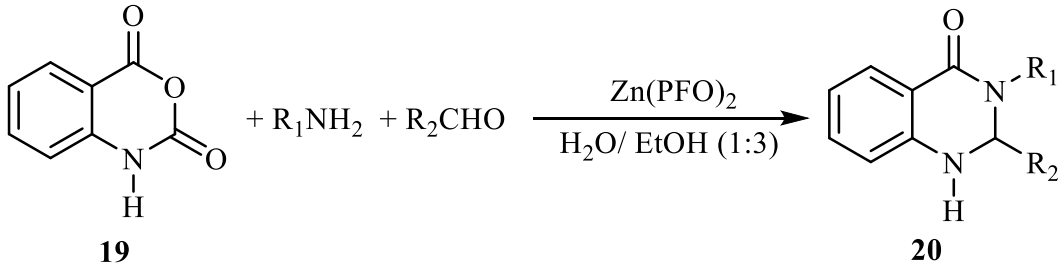
The aminoamides (**17**), obtained from the isatoic anhydrides (2H-3,1-benzoxazine-2,4-diones) (**16**), were cyclized using acetylenedicarboxylic esters to afford the diesters (**18**) (Figure 8)[46].



R_1= H, -Cl, -OCH_3; R_2= H,-OCH_3; R_1,R_2= -OCH_2O-; R_3= H, -CH_3;
R_4= -CH_3, $HOCH_2$, 2-ClC_6H_4, 4-ClC_6H_4, *t*-BuCO, -OCH_3; R_5= -CH_3, -C_2H_5.

Figure 8. Synthesis of compound **18** derivatives

Three-components one-pot cyclocondensation reaction of isatoic anhydride (**19**) with amines and aldehydes was conducted under the effect of zinc (II) perfluorooctanoate [$Zn(PFO)_2$] to afford the corresponding quinazolinone derivatives (**20**) in good yields (Figure 9)[47].



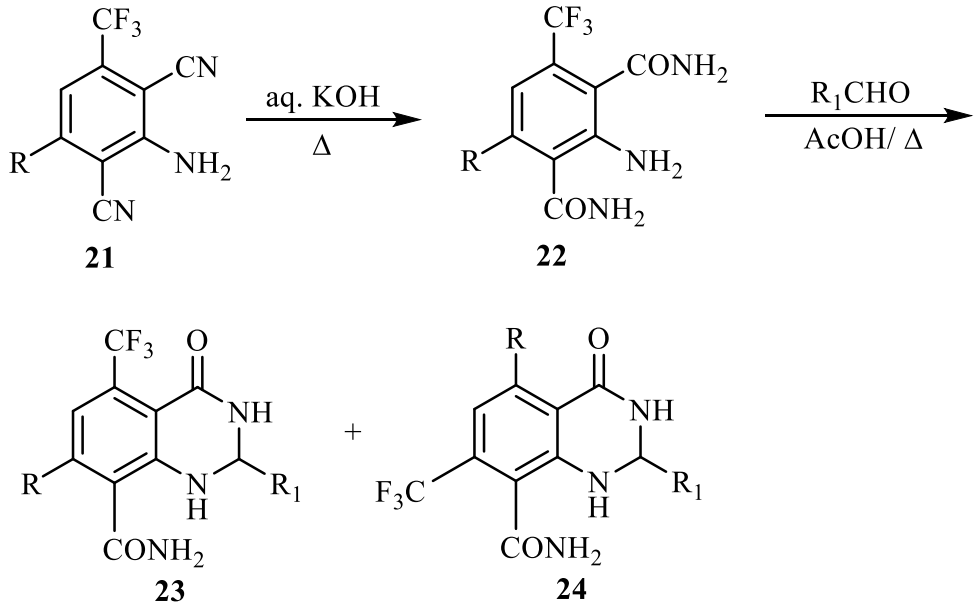
19 **20**

R_1, R_2= Different alkyl groups.

Figure 9. Synthesis of compound **20** derivatives

(C) *From Anthranilic Acid and Its Derivatives*

An interesting trifunctional intermediate (**21**) was hydrolyzed to give 2,6-dicarboxamido aniline (**22**) which was cyclized with different aldehydes to give two regioisomers of 1,2-dihydro-4(3*H*)-quinazolinones (**23**) and (**24**) (Figure 10)[48].



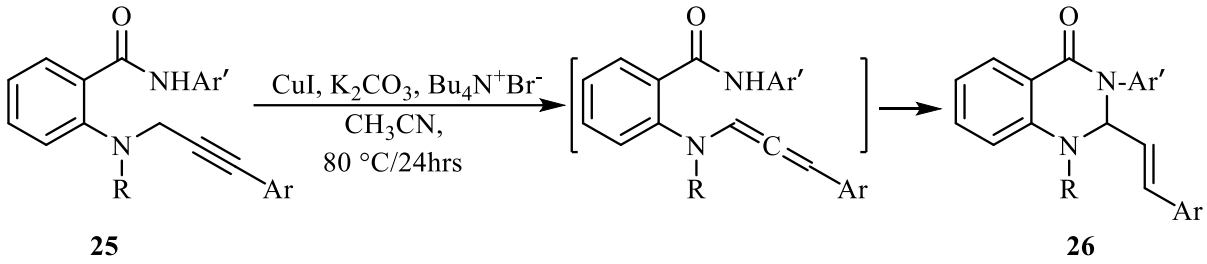
21 **22**

23 **24**

R,R_1= -CH_3, -C_6H_5.

Figure 10. Synthesis of compounds **23** and **24** derivatives

The alkyne derivatives (**25**) underwent a highly regio- and stereoselective cyclization in the presence of CuI, K_2CO_3 and n-$Bu_4N^+Br^-$ in acetonitrile to furnish the required quinazolinones (**26**) in good yields (Figure 11)[45].

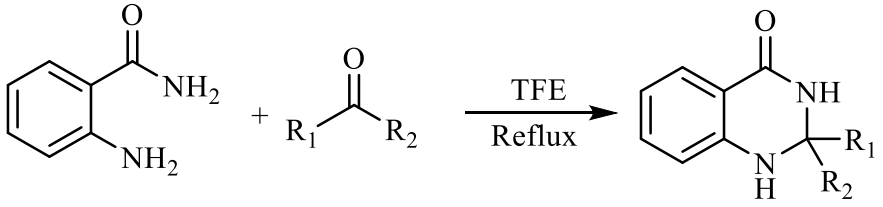


25 **26**

R= $-CH_3$, $-C_2H_5$; Ar, Ar′ = Different aromatic rings.

Figure 11. Synthesis of compound **26** derivatives

2-Substituted-2,3-dihydro-4(1*H*)-quinazolinones (**28**) were obtained in high yields by Qiao *et al.* through condensation of anthranilamide (**27**) with aryl, alkyl or heteroaryl aldehydes or ketones in the refluxing 2,2,2-trifluoroethanol (TFE) (Figure 12)[49].

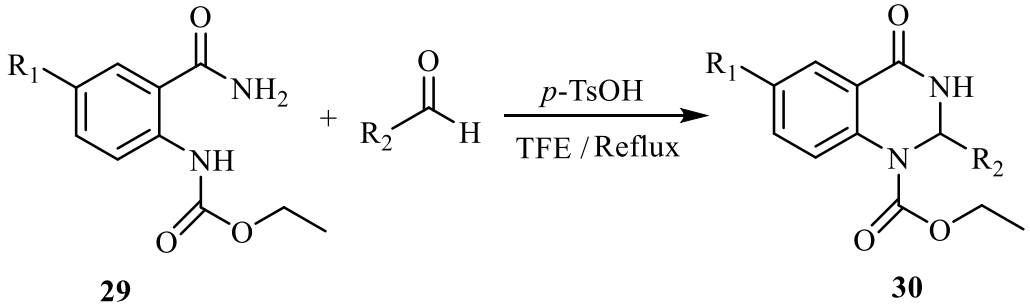


27 **28**

R_1= Aryl, heterroaryl, alkyl; R_2= H, Alkyl.

Figure 12. Synthesis of compound **28** derivatives

Ethyl 2,6-disubstituted-2,3-dihydro-4(1*H*)-quinazolinone-1-carboxylates (**30**) were developed by condensation of substituted ethyl (2-carbamoylphenyl)carbamate (**29**) with alkyl, aromatic or heteroaromatic aldehydes in TFE or hexa- fluoroisopropanol using *p*-toluenesulfonic acid as catalyst (Figure 13)[50].



29 **30**

R_1= H, NO_2, Cl; R_2= Phenyl, Substituted phenyl.

Figure 13. Synthesis of compound **30** derivatives

Anthranilic acid (**2**) and cyclohexanone were heated under reflux to give spiro[benzo[d][1,3]oxazine-2,1′-cyclohexan]-4(1*H*)-one (**31**) which reacted with the appropriate sulfa drugs in glacial acetic acid resulted in 4-(4′-oxo-1’H-spiro[cyclohexane-1,2′-quinazolin]-3′ (4′H)-yl)benzenesulfonamide (**32**) (Figure 14)[51].

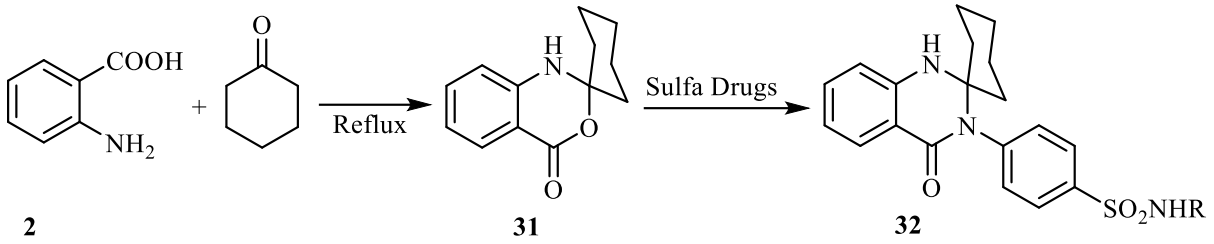
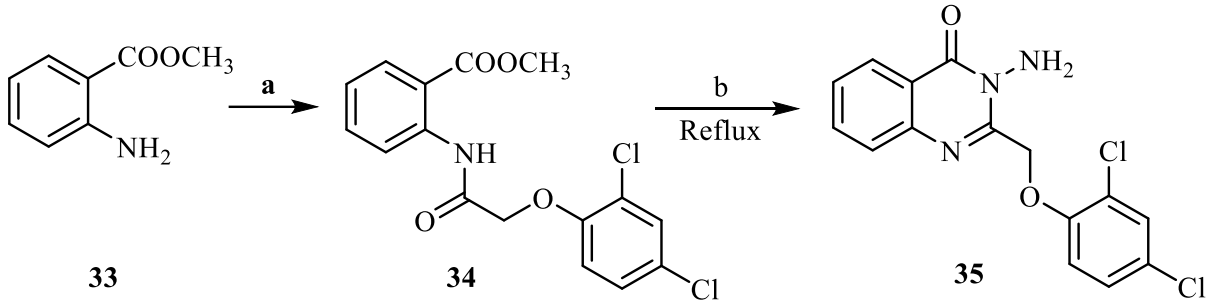


Figure 14. Synthesis of compound **32** derivatives

Moreover, Abbas S. E. *et al* synthesized 3-amino-2-(2,4-dichlorophenoxy)methyl-3,4-dihydroquinazolin-4-one (**35**) from methyl anthranilate (**33**) which was reacted with 2,4-dichlorophenoxyacetyl chloride to give the intermediate (**34**) followed by reflux with hydrazine hydrate in n-butanol (Figure 15)[52].



a= 2,4-dichlorophenoxyacetyl chloride, dry ether, TEA, rt 24h;
b= hydrazine hydrate (85%), n-butanol.

Figure 15. Synthesis of compound **35**

2.2. Chemistry of Benzotriazepines

Numerous isomeric ring systems are possible in the seven-membered rings with three heteroatoms (triheteroepines), depending upon the type and the relative positions of the three heteroatoms and the degrees of unsaturation. For benzotriazepines, there are five classes based on the position of the three nitrogen atoms: 1,2,3-Benzotriazepine (**36**), 1,2,4-benzotriazepine (**37**), 1,3,4-benzotriazepine (**38**), 1,2,5-benzotriazepine (**39**), and 1,3,5-benzotriazepine (**40**) (Figure 16)[53].

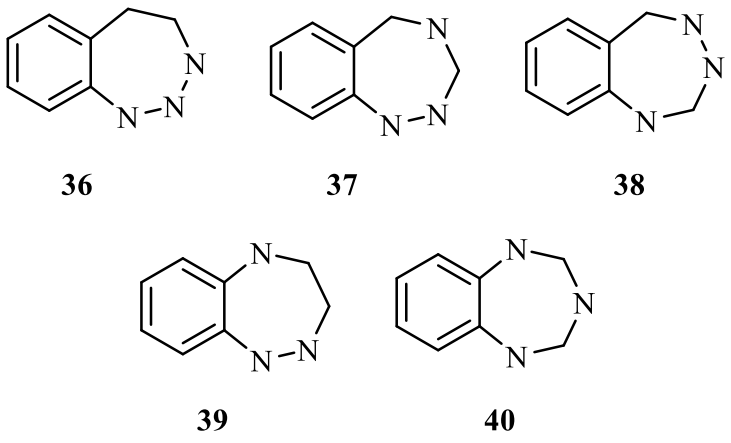


Figure 16. Classes of benzotriazepines

The present part represent a brief outline of different methods for preparation of benzotriazepines especially 1,3,4-type.

(A) From Isatoic Anhydrides

Anthranilic acid hydrazide (**41**) obtained from isatoic anhydride represents a good precursor for 1,3,4-benzotriazepine, since its cyclization with active carbonyl compounds as phosgene or ethyl chloroformate afforded 1,3,4-benzotriazepinedione (**42**)[54-56]. Similarly, the intermediate (**41**) was cyclized upon using aldehydes or ortho ester to afford the benzotriazepine (**43)** or (**44**) (Figure 17)[54,56-57].

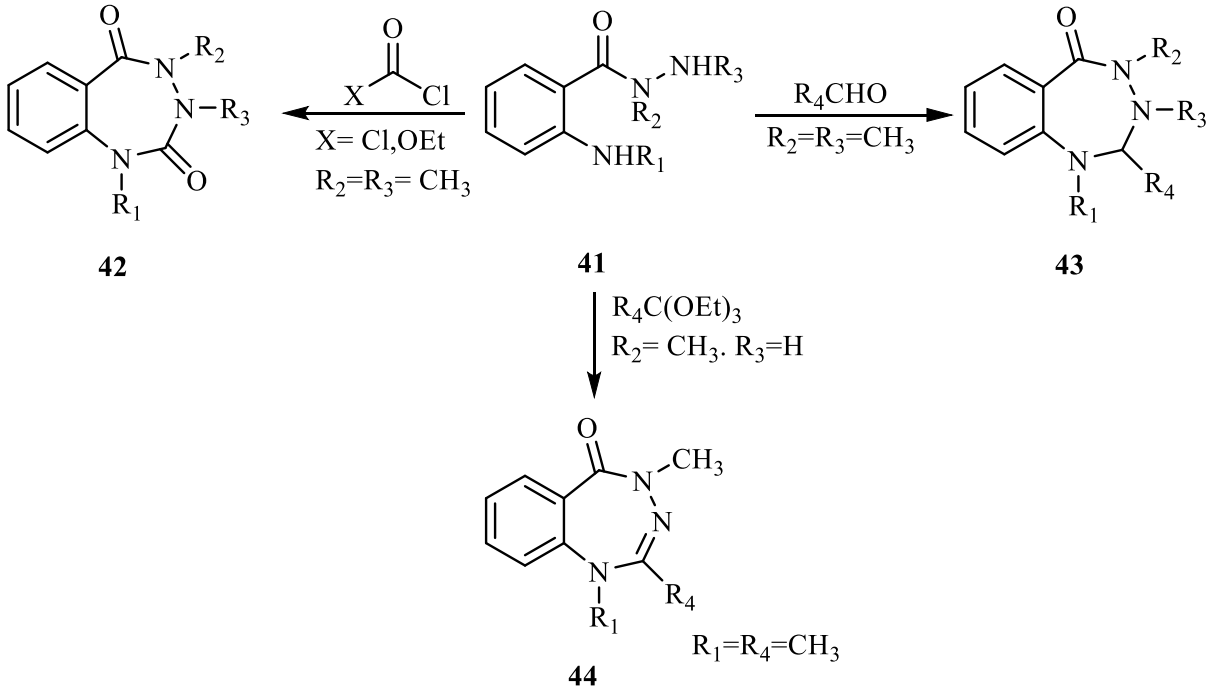
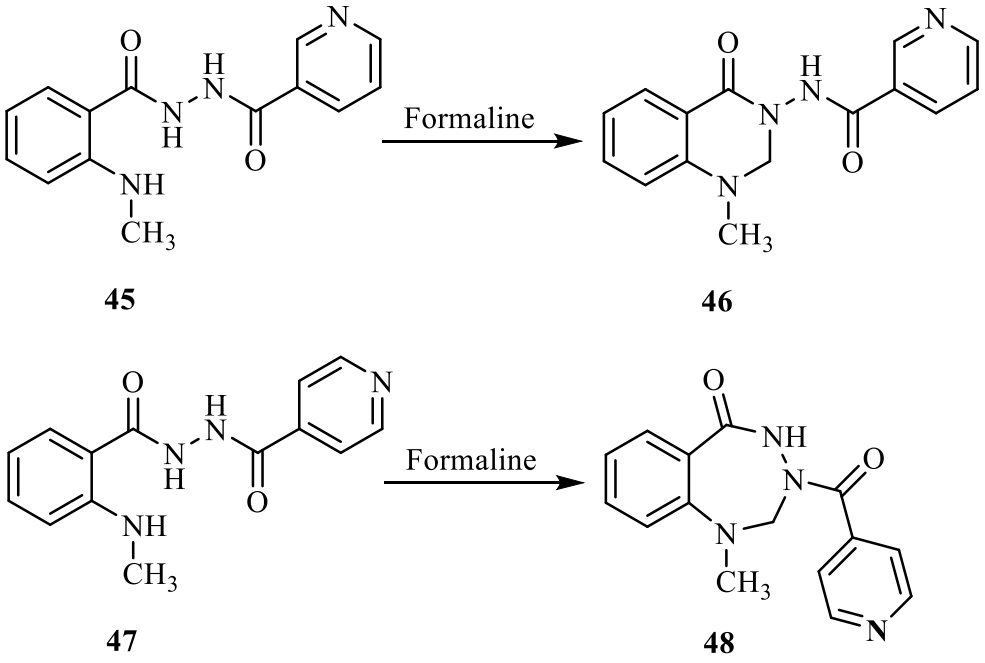


Figure 17. Synthesis of compounds **42**, **43** and **44** derivatives

Cyclization of N′-(2-(methylamino)benzoyl)nicotinohydrazide (**45**) with formaline/acetic acid resulted in formation of *N*-(1-methyl-4-oxo-1,2-dihydroquinazolin-3(4H)-yl)nicotinamide (**46**). Whereas, by cyclization of *N*-(2-(methylamino)benzoyl)isonicotinohydrazide (**47**) with formaline/acetic acid, the 3-isonicotinoyl-1-methyl-3,4-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-one (**48**) was obtained (Figure 18).[58]



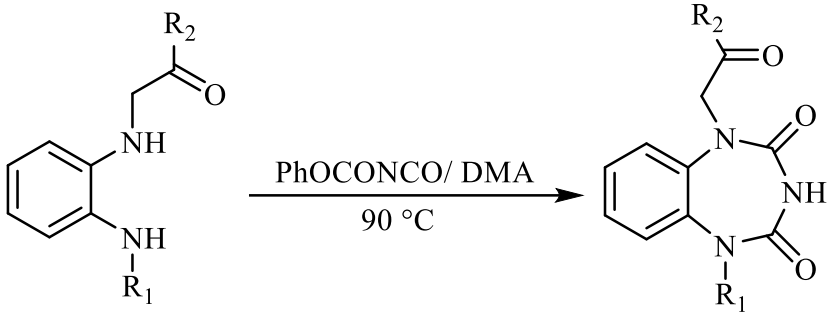
45 **46**

47 **48**

Figure 18. Synthesis of compounds **46** and **48**

(B) From Diamines

Treatment of asymmetrically alkylated diamines **(49)** with phenyl isocyanatoformate led to the formation of 1,3,5-benzotriazepine-2,4-dione derivatives **(50)** (Figure 19)[59].



49 **50**

R_1= Ph, c-C_6H_{11}, c-C_7H_{13};
R_2= OBu, Pyrrolidin-1-yl, *t*-Bu.

Figure 19. Synthesis of compound **50** derivatives

2-[(2-Aminophenylimino] imidazolidines (**51**) were subjected to react with a variety of aldehydes and ketones in the presence of $ZnCl_2$ at room temperature to give the complexes (**52**) which under the effect of methanolic NaOH solution gave 1,2,3,5-tetrahydroimidazo[2,1-b] [1,3,5] benzotriazepines (**53**) (Figure 20)[60].

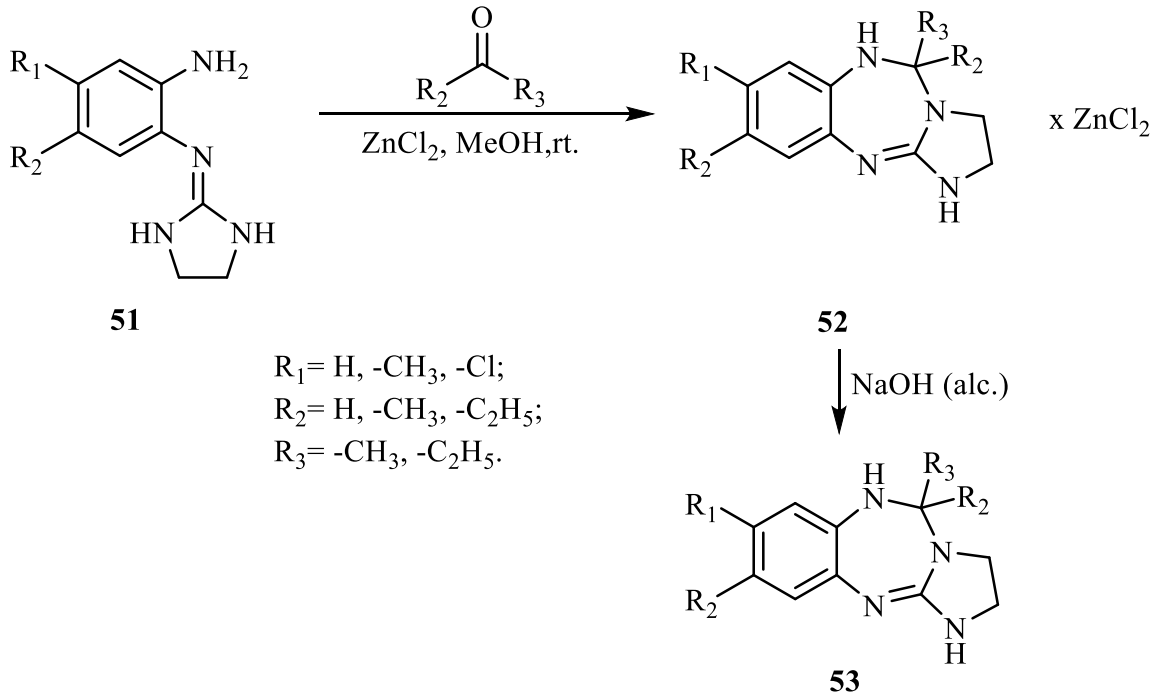


Figure 20. Synthesis of compound **53** derivatives

(C) From Thiosemicarbazide Intermediates

The thiosemicarbazide intermediates (**55**),which were synthesized by treating 2-benzoylphenylisothiocyanates (**54**) with hydrazine hydrates, were cyclized under the effect of heat in n-propanol solvent to give the benzotriazepines (**56**) (Figure 21)[61].

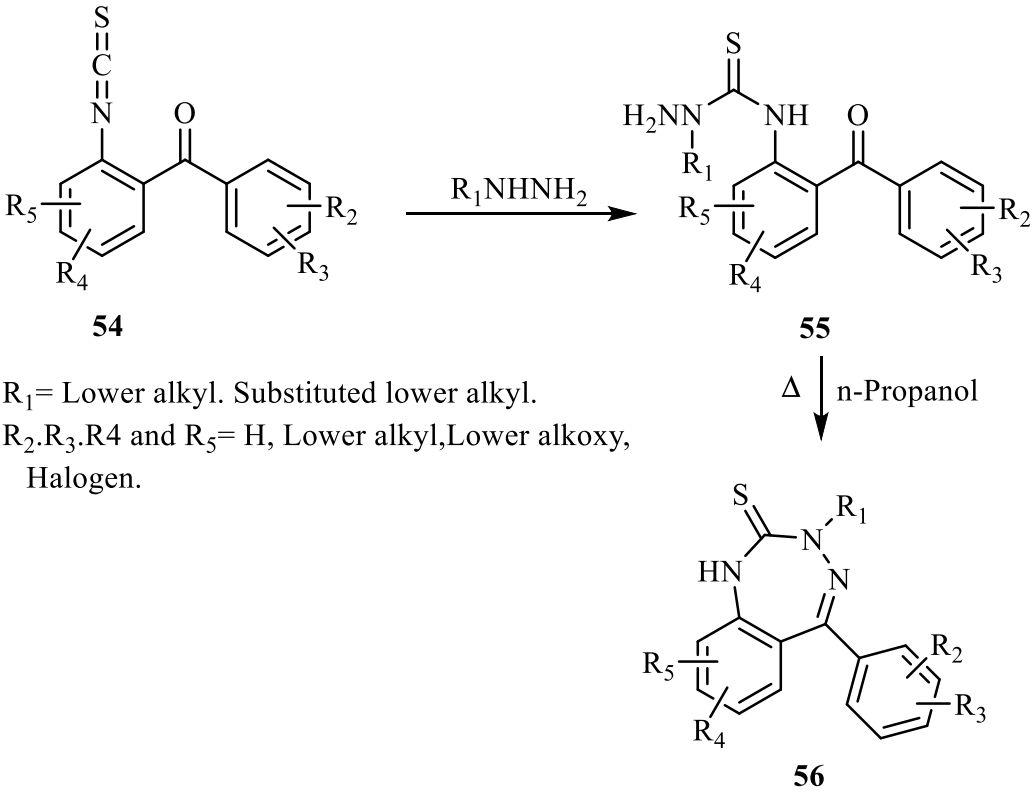


Figure 21. Synthesis of compound **56** derivatives

(D) From Other Heterocyclic Compounds

Alexandre *et al* described the synthesis of substituted 1,3,4-triazepine-2,5-diones (**58**) starting from 4-oxo-4H-benzo[d][1,3]oxazine-2-carbonitrile (**57**) (Figure 22)[62].

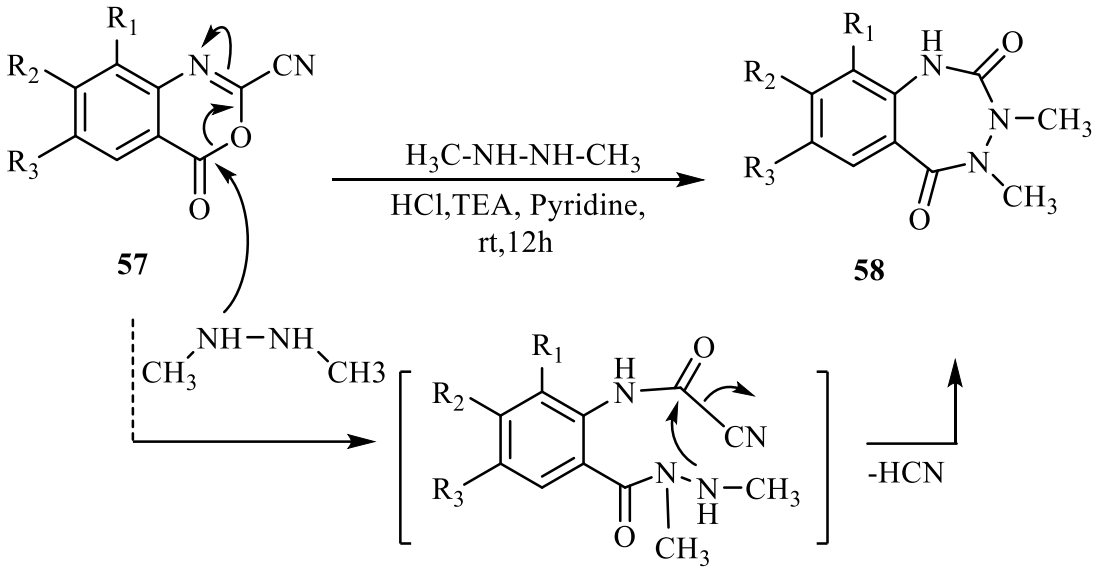


Figure 22. Synthesis of compound **58** derivatives

(E) From Anthranilic Acid Derivatives

Benzo[e][1,2,4]triazepines (**63**) were synthesized starting from compound (**59**) as in the following (Figure 23)[63]:

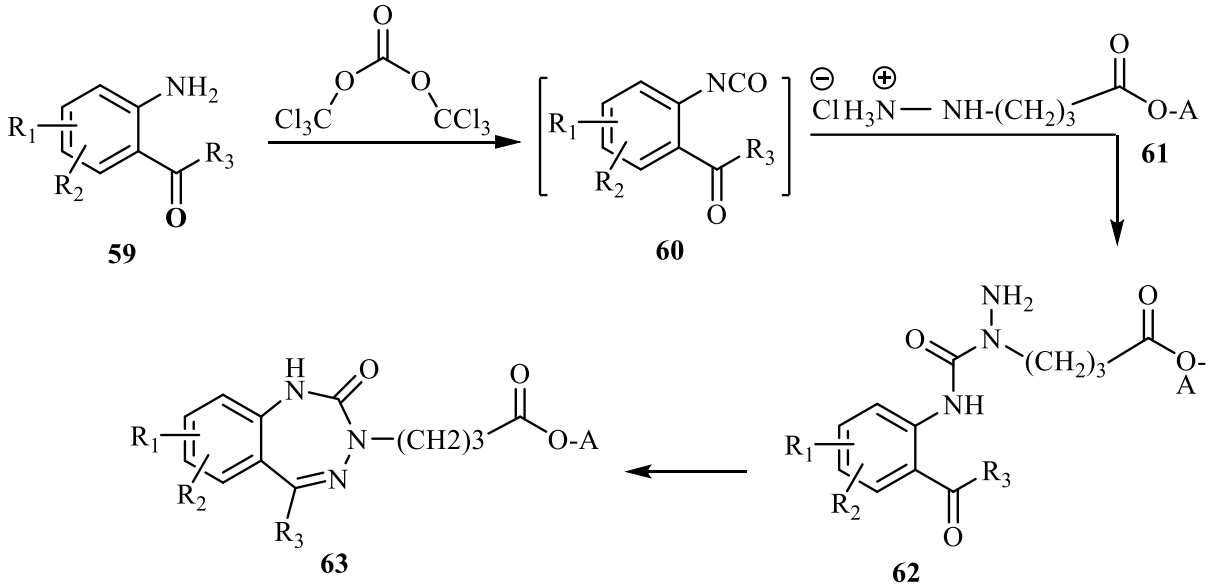
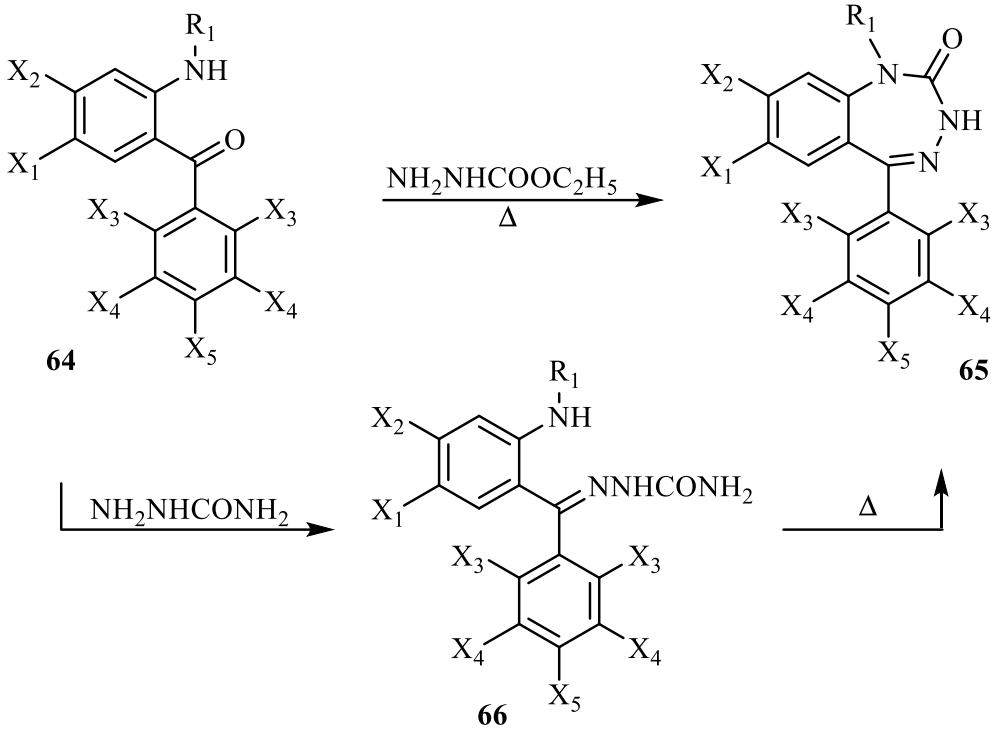


Figure 23. Synthesis of compound **63** derivatives

The benzotriazepines (**65**) were prepared from the commercially available intermediates (**64**) and ethyl carbazide or from the corresponding hydrazones (**66**) at elevated temperatures (Figure 24)[64].



X_{1-5}=H, Halogen, C_{1-4} alkyl, hydroxyl, amino.
R_1= H, C_{1-4} alkyl, C_{1-4} alkenyl.

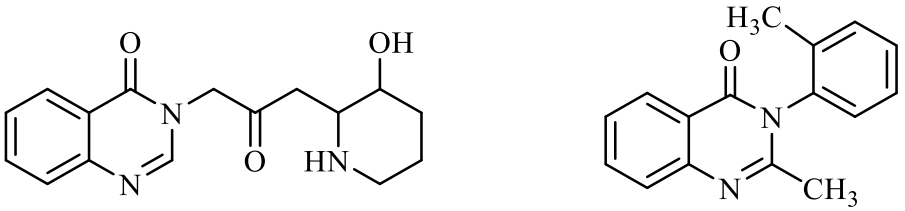
Figure 24. Synthesis of compound **65** derivatives

3. Biological activity

3.1. Biological Activity of 4(3H)-Quinazolinones

3.1.1. Historical Overview

Interest in the medicinal chemistry of quinazoline derivatives was stimulated in the early 1950's with the elucidation of a quinazoline alkaloid, 3-[β-keto-γ(3-hydroxy-2-piperidyl)-propyl]-4-quinazolinone (**67**), from an Asian plant known for its antimalarial properities. In a quest to find additional antimalarial agents, various substituted quinazolines have been synthesized, of particular importance was the synthesis of the derivative 2-methyl-3-*o*-tolyl-4-(3*H*)-quinazolinone (**68**).This compound, known by the name methaqualone, though ineffective against protozoa,was found to be a potent hypnotic[65]. Since the introduction of methaqualone and its discovery as a hypnotic, the pharmacological activity of quinazolinones and related compounds has been investigated (Figure 25).



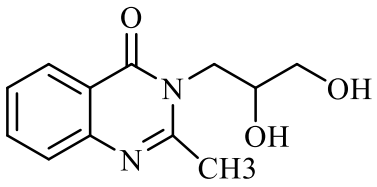
67 **68**

Figure 25. Structure of compounds **67** and **68**

Quinazolinones and their derivatives therefore are now known to have a wide variety of biological properities including anti-inflammatory, antitumer, antimicrobial, hypnotic, sedative, analgesic and anticonvulsant effects[66].

(A) Anti-Inflammatory Activity

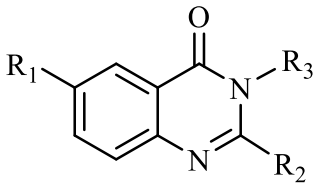
Diproqualone (Algopriv®, **69**), 4(3*H*)-quinazolinone derivative, is a well known drug which used primarily for the treatment of inflammatory pain associated with osteoarthritis (Figure 26)[67].



69

Figure 26. Structure of diproqualone

Santagati *et al* synthesized a series of 4(3*H*)-quinazolinone derivatives (**70**) which significantly reduced prostaglandin E2 (PGE2) levels even more than the reference drug tolmetin and significantly lower protein concentration and polymorphonuclear leukocytes number compared to the control group (Figure 27)[68].

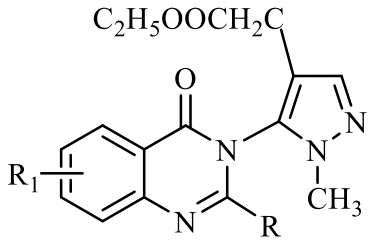


70

R_1= H, Cl; R_2, R_3= H, -CH_3, -C_6H_5.

Figure 27. Structure of compound **70** derivatives

Moreover, several new ethyl 1-methyl-5-(substituted 3,4-dihydro-4-oxoquinazolin-3-yl)-1*H*-pyrazol-4-acetate (**71**) were synthesized and some of them showed appreciable anti-inflammatory activity with low ulcerogenic index (Figure 28)[69].

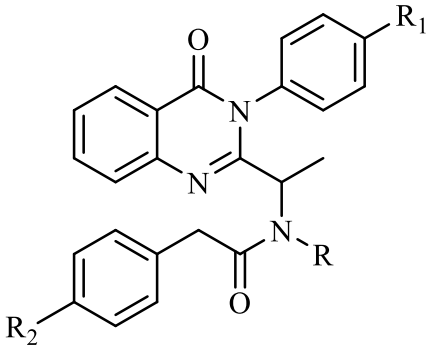


71

R= H, -CH_3, -C_2H_5, -C_6H_5; R_1= 6-Cl, 7-Cl, 8-CH_3.

Figure 28. Structure of compound **71** derivatives

A series of 4(3*H*)-quinazolinones **72** were developed and found to be useful in treatment of rheumatoid arthritis and inflammatory bowel diseases (Figure 29)[70].

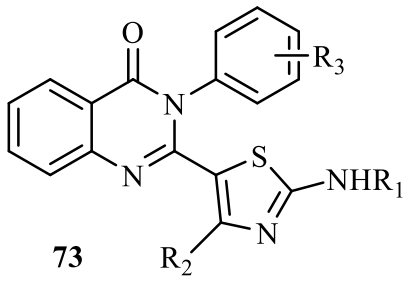


72

R= -$(CH_2)_2N(CH_3)_2$, -$(CH_2)_2OMe$, $(CH_2)_2OEt$, -$(CH_2)_2CH_3$,CH_2-2-thiazolyl,
-CH_2-2-pyridyl, -CH_2-4-(1-Methyl-imidazolyl.
R_1= -F, -OEt, -Cl, -CH_3; R_2= -CF_3, phenyl.

Figure 29. Structure of compound **72** derivatives

In addition, a series of 2-(2,4-disubstituted-thiazol-5-yl)-3-aryl-4(3*H*)-quinazolinone derivatives (**73**) were synthesized and most of them exhibited significant efficacy in vivo model of inflammation (Figure 30)[71].

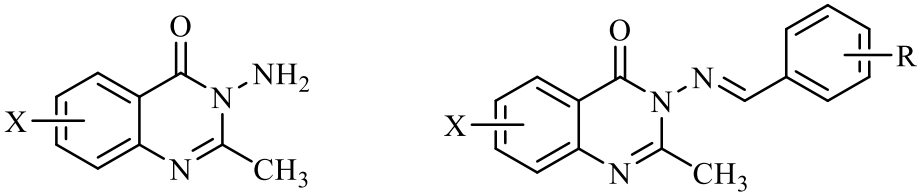


73

R= -CH_3, -C_6H_4, *p*-ClC_6H_4, *p*-$CH_3C_6H_4$.
R_2= -CH_3, -C_6H_5, -NH_2 ; R_3= H, -Cl, -CH_3, -OCH_3, -$COCH_3$.

Figure 30. Structure of compound **73** derivatives

2-Methyl-3-amino-4(3*H*)-quinazolinone (**74**) and 2-methyl-3-(arylidene-amino)-4(3*H*)-quinazolinone (**75**) derivatives were synthesized and found to exhibit anti-inflammatory activity at a dose level of 50 mg/kg. in varying degree from 16.3 to 36.3% inhibition of edema (Figure 31)[72].

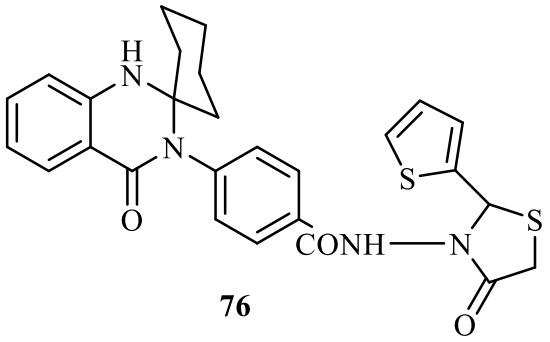


74 **75**

X= H, 6-Br; R= H, *p*-Cl, *p*-OH, *p*-OCH_3.

Figure 31. Structure of compounds **74** and **75** derivatives

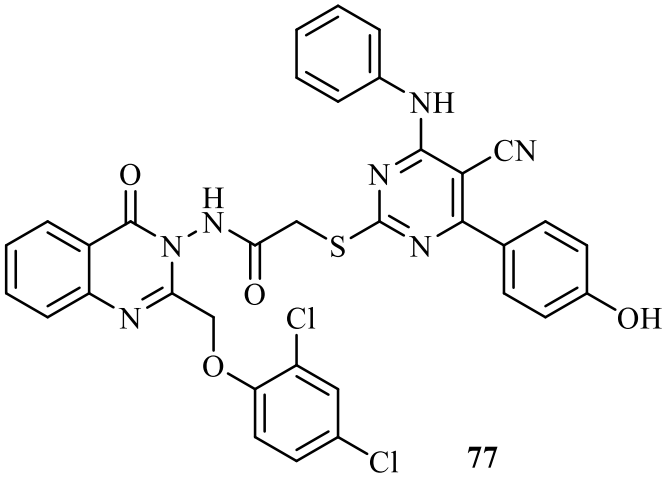
A novel series of spiro[(2H,3H)quinazoline-2,1cyclohexan]-4(1H)–one derivatives were synthesized and evaluated as anti-inflammatory and analgesic activities. It is observed that compound (**76**) showed the greatest activity and G.I.T. safety profile in experimental rats among this series (Figure 32)[51].



76

Figure 32. Structure of compound **76**

2-[5-Cyano-6-(4-hydroxyphenyl)-4-phenylaminopyrimidin-2-yl-sulfanyl]-N-[2-(2,4-dichlorophenoxymethyl)-4-oxo-4H-quinazolin-3-yl]acetamide (**77**) was synthesized and evaluated as anti-inflammatory (selective inhibitors to COX-2) and it was found that compound was the most active and the safest one (Figure 33)[52].

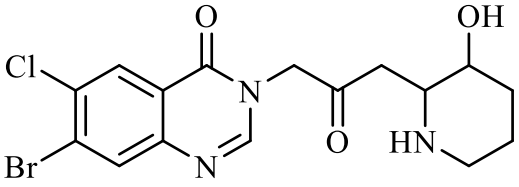


77

Figure 33. Structure of compound **77**

(B) Antitumor Activity

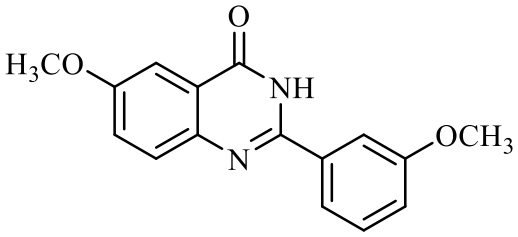
Halofuginone (Tempostatin®, **78**) is a synthetic derivative of a quinazolinone alkaloid showing anti-angiogenic, anti-metastatic and anti-proliferative effects in preclinical studies (Figure 34)[73].



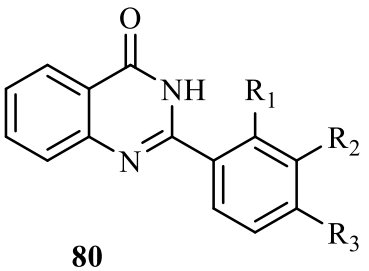
78

Figure 34. Structure of halofuginone

The 4(3*H*)-quinazolinone (**79**) displayed significant growth inhibitory action against a panel of tumor cell lines and it was found to be a potent inhibitor of tubulin polymerization. 4(3*H*)-Quinazolinone derivatives (**80**) displayed selective activity against epidermoid carcinoma of the nasopharynx (Figure 35)[74].



79

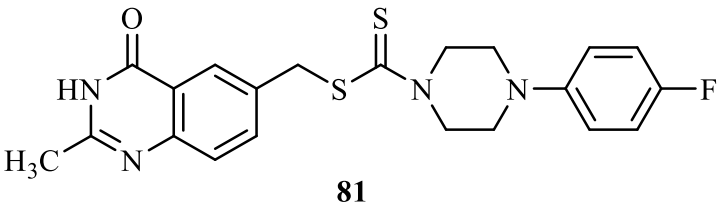


80

R_1=H, F; R_2= H,F; R_3=H, F.

Figure 35. Structure of compounds **79** and **80** derivatives

Moreover, a series of 4(3*H*)-quinazolinone derivatives with dithiocarbamate side chain were synthesized and tested for their *in vitro* antitumor activity against human myelogenous leukemia (K562) cells. Among them, compound **81** exhibited significant inhibitory activity against K562 cells (Figure 36)[75].



81

Figure 36. Structure of compound **81**

Compound **82** exhibited a significant antitumor activity. Also, among quinazoline analogs to methotrexate (MTX) structure, compound **83** was found to be the most active one as antitumor agent (Figure 37)[76].

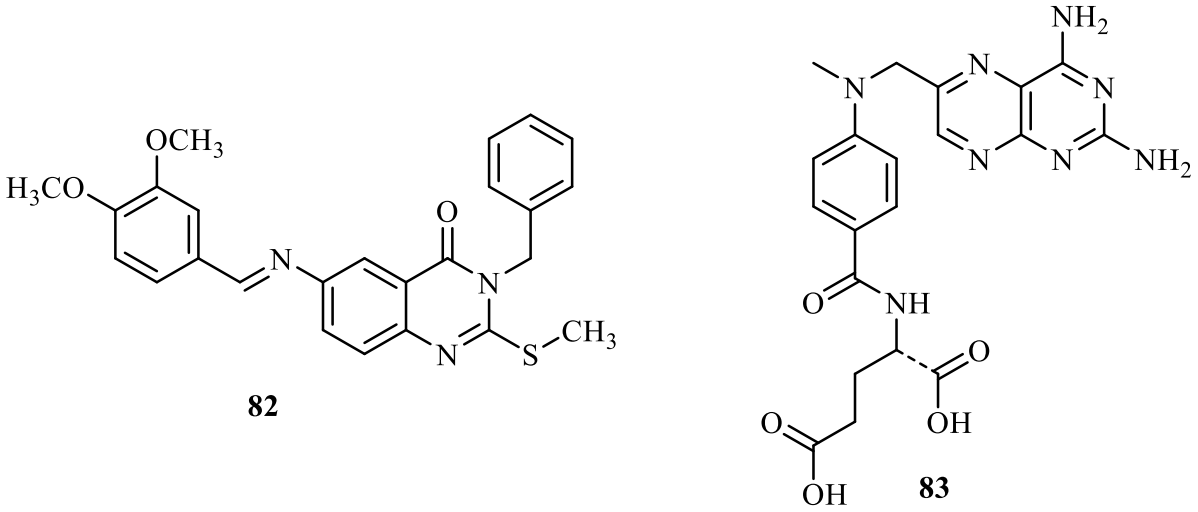


Figure 37. Structure of compounds **82** and **83**

Some 2-(thiophen-2-yl)quinazolin-4(3*H*)-one derivatives were prepared and their biological study as antitumor agents revealed that compound **54** was the most active as compared to the clinically used drug 5-fluorouracil (Figure 38)[77].

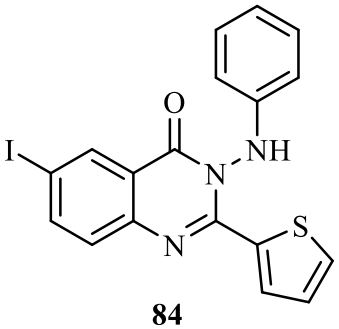


Figure 38. Structure of compound **84**

Converso *et al* succeeded in the synthesis of a thioquinazolinone series, among them compound **85** showed great antitumor activity (Figure 39)[78].

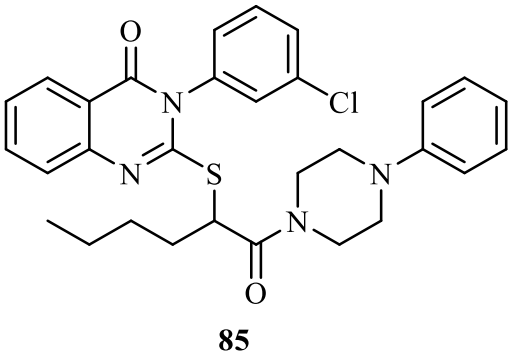
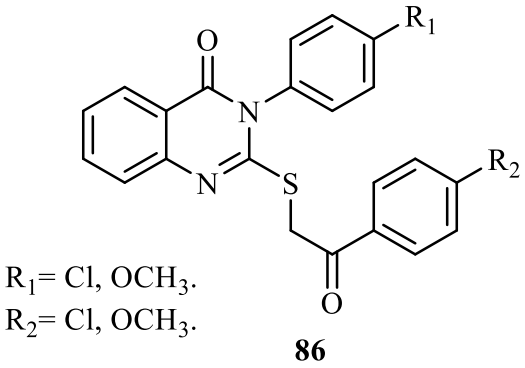


Figure 39. Structure of compound **85**

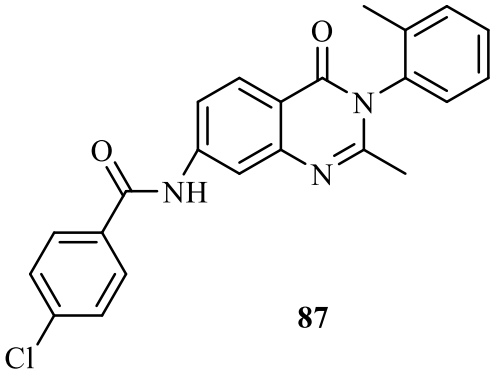
Some 2,3-disubstituted quinazolin-4(3*H*)-ones were synthesized and evaluated for their anti-tumor activity, among them compound **86** showed great antitumor activity (Figure 40)[79].



86

Figure 40. Structure of compound **86** derivatives

A novel series of 7-substituted-4(3*H*)-quinazolinone were designed, synthesized and evaluated for their antitumor activity. Compound **87** revealed broad-spectrum antitumor effectiveness toward numerous cell lines that belong to different tumor subpanels (Figure 41)[80].

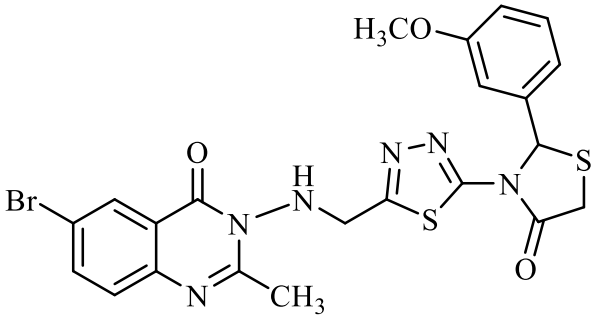


87

Figure 41. Structure of compound **87**

(C) Central Nervous System Activity

A series of 4(3*H*)-quinazolinones bearing 1,3,4-thiadiazole and thiazolidinone moieties have been synthesized and screened for their anticonvulsant activity. It was found that compound **88** was the active one in comparison with phenytoin sodium, lamotrigine and sodium valproate as standard drugs (Figure 42)[81].

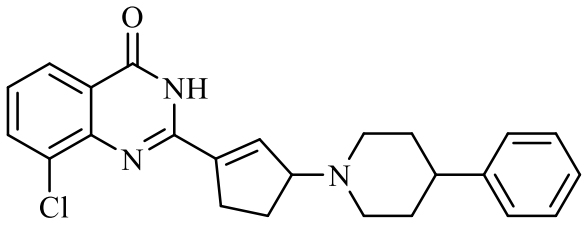


88

Figure 42. Structure of compound **88**

A successful design of conformationally restricted novel quinazolinone derivatives linked via a cyclopentene moiety as potent poly(ADP-ribose)polymerase-1 (PARP-1) inhibitors has been developed,

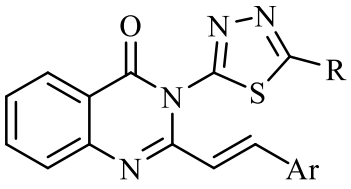
and 8-chloro-2-[(3S)-3-(4-phenylpiperidin-1-yl)cyclopent-1-en-1-yl]quinazolin-4(3*H*)-one (**89**), was found to be highly potent and a good brain penetration (Figure 43)[82].



89

Figure 43. Structure of compound **89**

Moreover, a series of 4(3*H*)-quinazolinones carrying 1,3,4-thiadiazole derivatives (**90**) were synthesized and evaluated for their anticonvulsant, sedative and hypnotic activities. Some of them showed anticonvulsant as well as sedative-hypnotic activities (Figure 44)[83].

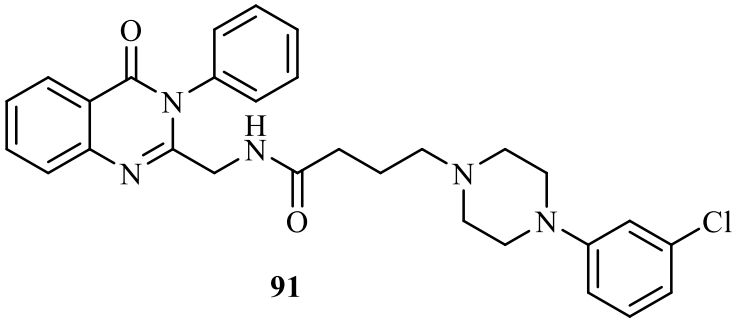


R= -C_6H_5, *p*-ClC_6H_4, *m*-ClC_6H_4.
Ar= -C_6H_5, *p*-$OCH_3C_6H_4$.

90

Figure 44. Structure of compound **90** derivatives

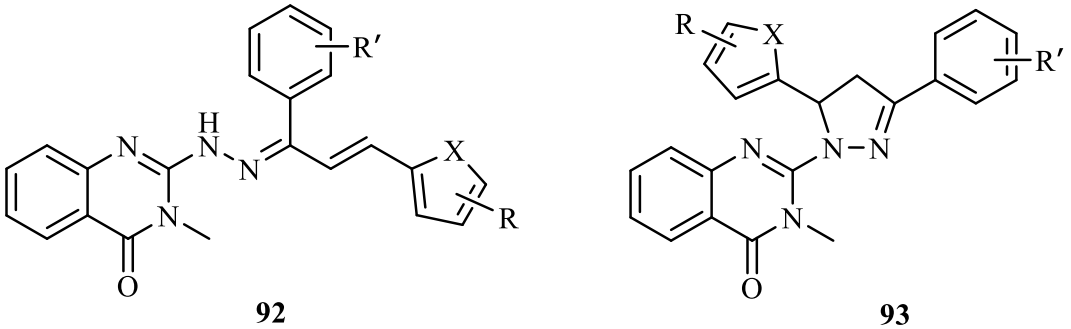
Also, a new series of 4(3*H*)-quinazolinones having aminobutyramide moiety characteristic for the neuroleptics was prepared. Among them compound **91** was found to exhibit antagonistic activity to 5-HT_7 receptor leading to antidepressant-like effects (Figure 45)[84].



91

Figure 45. Structure of compound **91**

In addition, new series of pyrazoline, bearing 4(3*H*)-quinazolinone derivatives were prepared starting from a quinazolinone ring and evaluated for their MAO-A and -B inhibitory activities. Some of the synthesized compounds **92** and **93** showed high activity against both MAO-A and MAO-B isoforms. MAO-A inhibitors have been used mostly in the treatment of mental disorders, in particular depression and anxiety while MAO-B inhibitors could be used in the treatment of Parkinson's disease and perhaps, Alzheimer's disease (Figure 46)[85].

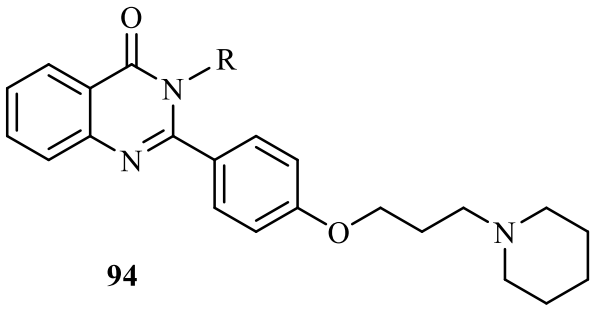


92 **93**

R′= -CH_3, -Cl, -OCH_3; R= H, 3Cl, 4-Cl, 4-Br, 4-CH_3, 3-OCH_3, 3,4-di-OCH_3, 4-OCH_3, X=S,O.

Figure 46. Structure of compounds **92** and **93** derivatives

Several 2-[4-(aminoalkoxy)phenyl]-4(3*H*)-quinazolinone derivatives **(94)** were prepared and found to be a potent human H_3 receptor inverse agonists (Figure 47)[86].

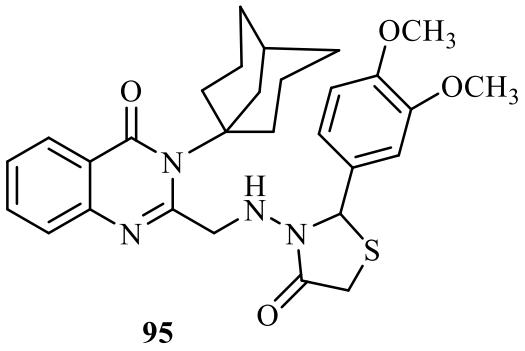


94

R= -CH_3, -C_2H_5, -C_6H_5, -$C_6H_5CH_2$.

Figure 47. Structure of compound **94** derivatives

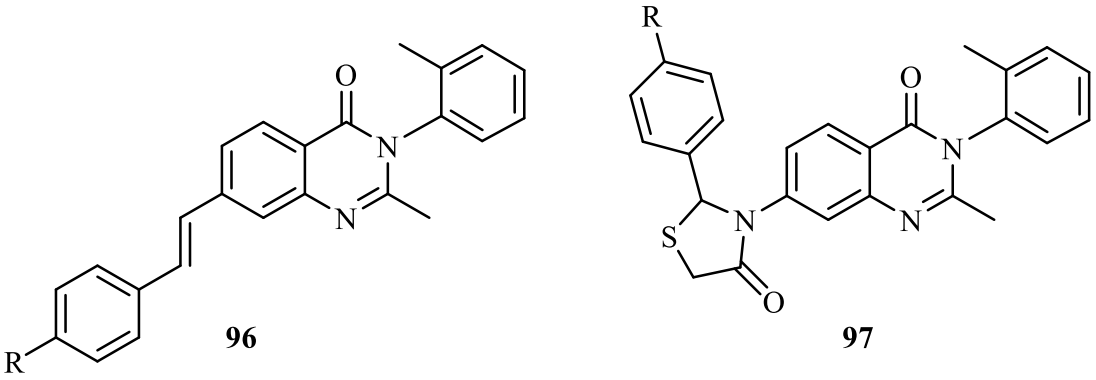
Several 3-((3-(3,7-dimethylbicyclo[3.3.1]nonan-1-yl)-4-oxo-3,4-dihydroquinazolin-2-yl) methylamino)-2-phenylthiazolidin-4-ones were prepared and screened for their antiparkinsonian activity, and it was found that compound **95** is the most active one among this series (Figure 48)[87].



95

Figure 48. Structure of compound **95**

A novel series of 7-substituted-4(*3H*)-quinazolinone were designed, synthesized and evaluated for anticonvulsant activity. It was observed that compounds **96** and **97** showed anticonvulsant activity as well as lower neurotoxicity than reference drugs (Figure 49)[80].



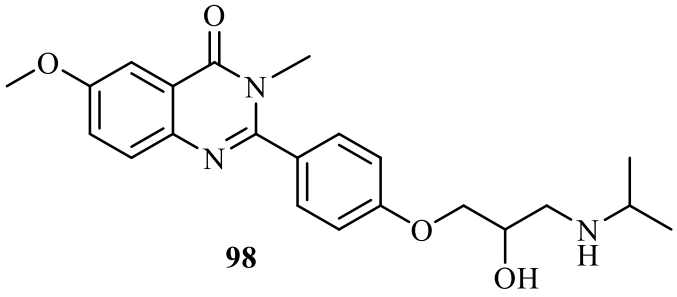
96 **97**

R= F,Cl R= H,F,Cl

Figure 49. Structure of compounds **96** and **97** derivatives

(D) Cardiovascular System Activity

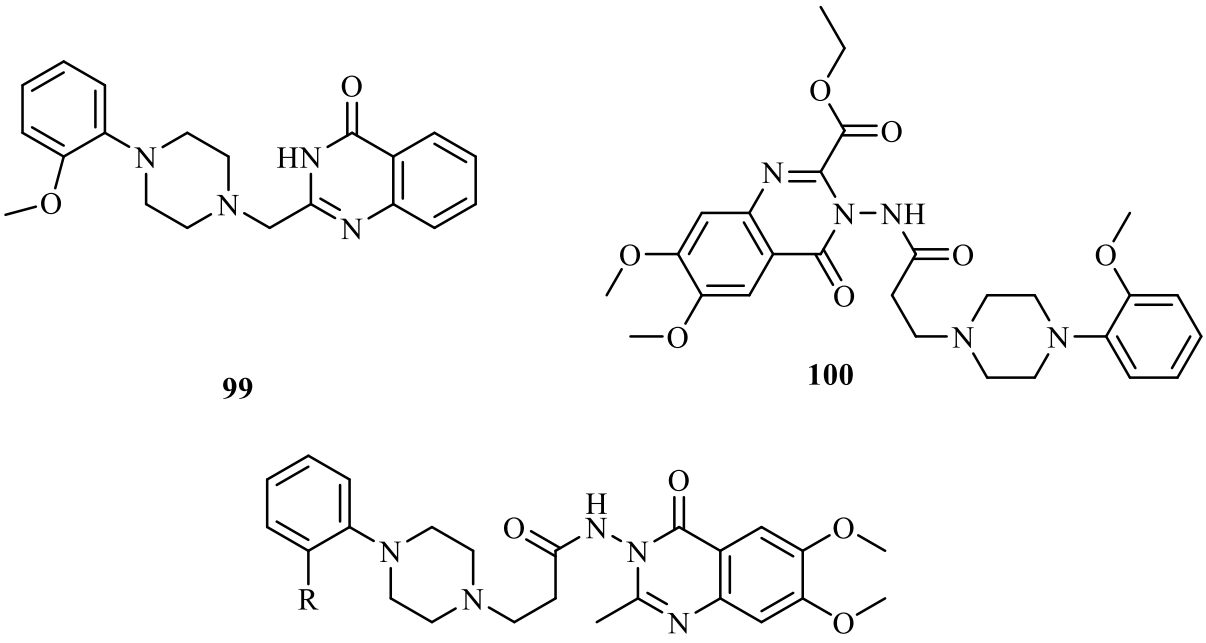
A new series of N-isopropyl and N-fluoroisopropyl derivatives of the β1-adrenergic receptor antagonist. Among them, 2-(4-(3-(tert-butylamino)-2-hydroxypropoxy)phenyl)-6-methoxy-3-methylquinazolin-4(3*H*)-one (**98**) was well synthesized and it is found to be selective towards β1-adrenergic receptors (Figure 50)[88].



98

Figure 50. Structure of compound **98**

Moreover, three series of new 2-[(4-substitutedpiperazin-1-yl) methyl]quinazolin-4(3*H*)-ones, ethyl 6,7-dimethoxy-4-oxo-3-[2-(4-substitutedpiperazin-1-yl)acetamido/propanamido]-3,4-dihydro-quinazoline-2-carboxylates and their 2-methyl analogues (**99**), (**100**), and (**101**) were designed and synthesized as promising α1-adrenoceptor antagonists[89]. These compounds were evaluated for their in vivo hypotensive activity in normotensive cats, and all were found to be active (Figure 51).



99 **100**

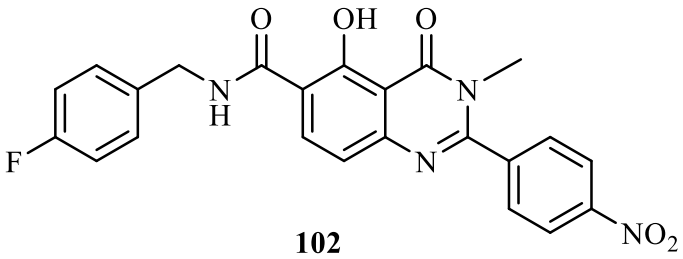
101

R= H, -OCH_3.

Figure 51. Structure of compounds **99**, **100** and **101** derivatives

(E) Antiviral Activity

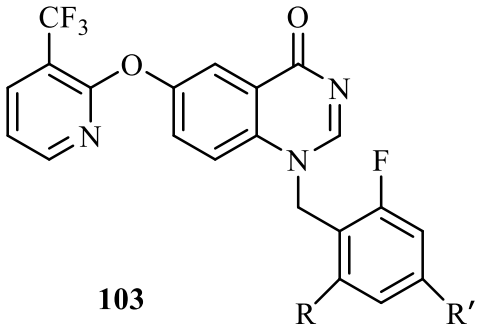
A series of novel quinazolinones (**102**) have been prepared as HIV-1 inhibitors (Figure 52)[90].



102

Figure 52. Structure of compound **102**

Recently, a new series of 1-benzylquinazolin-4-one derivatives were synthesized and it was found to be inhibitors of the virally-encoded NS5B RNA-dependent RNA polymerase of the hepatitis C virus. Compound **103** showed the greatest activity (Figure 53)[91].



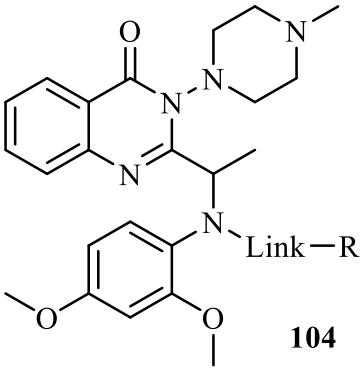
103

R= -Cl, -CH_3, F; R′= H,-F.

Figure 53. Structure of compound **103** derivatives

(F) Antimicrobial Activity

A series of 4(3*H*)-quinazolinone (**104**) was synthesized and most of them showed potent activity against both *Candida albicans* and *Candida glabrata* (Figure 54)[92].

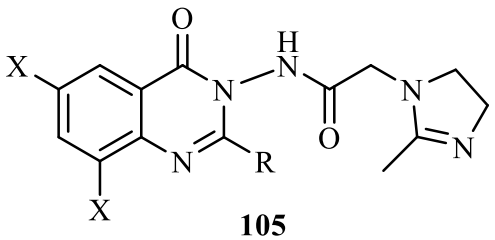


104

Link= -$CONH_2$, CO_2, SO_2; R= 3-ClC_6H_4, 4-$OMeC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4.

Figure 54. Structure of compound **104** derivatives

Several 2-(2-methyl-4,5-dihydro-1*H*-imidazol-1-yl)-N-(4-oxoquinazolin-3(4*H*)-yl)acetamides (**105**) were synthesized and subjected to antimicrobial activity against variety of pathogenic bacteria and fungi. The antimicrobial screening revealed that some of the compounds are moderately active against *Bacillus subtilis* and *Pseudomonas aeruginosa* (Figure 55)[93].



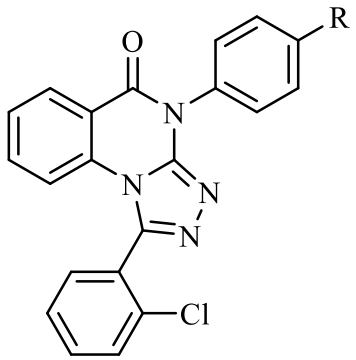
105

X= H, -Br; R=-CH_3, -C_3H_7, -C_6H_5.

Figure 55. Structure of compound **105** derivatives

Series of fused heterocyclic systems, triazolo[4,3-a]-quinazolin-5- ones have been synthesized and screened for their antibacterial activity, as well as antifungal activity against different fungi. The

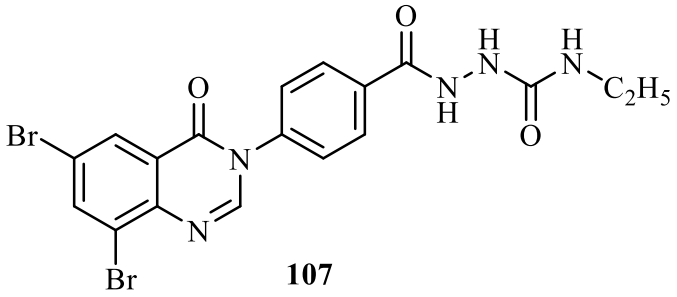
study revealed that compound **106** derivatives were the most active compounds against fungi, *Aspergillus fumigatus*, *Aspergillus flavus*, Gram-negative bacteria, *Escherichia coli*, *Pseudomonas aeruginosa* and Gram-positive bacteria, *Streptococcus pneumoniae*, *Bacillus subtilis* (Figure 56)[94].



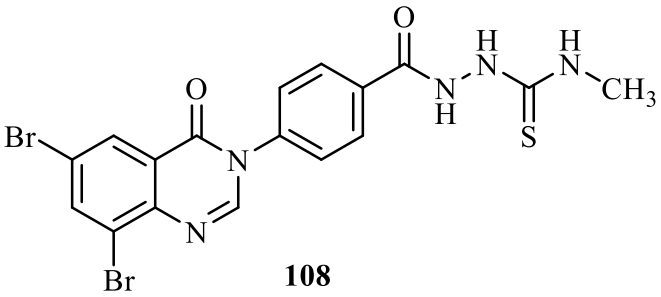
106 R= -Cl, -OCH_3.

Figure 56. Structure of compound **106** derivatives

Novel 6,8-dibromo-4(3*H*)quinazolinone derivatives synthesized and evaluated for their anti-bacterial and anti-fungal activities, compound (**107**) was found to exhibit the most potent in vitro anti-microbial activity with the MICs of 1.56, 0.39, 1.56, 1.56, 0.78 and 0.39 µg/ml against *E.coli*, *S.typhimurium*, *L.monocytogenes*, *S. aureus*, *P.aeruginosa*, *and B. cereus* respectively[95]. Also, Compound (**108**) was found to exhibit the most potent in vitro anti-fungal activity with MICs 1.56 and 0.78µg/ml against *C.albicans* and *A. flavus* (Figure 57).



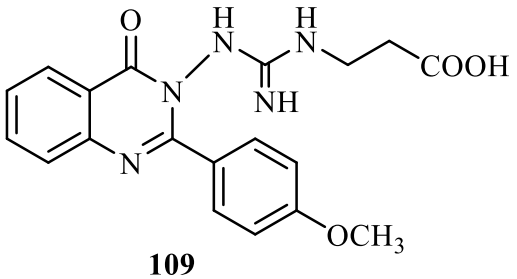
107



108

Figure 57. Structure of compounds **107** and **108**

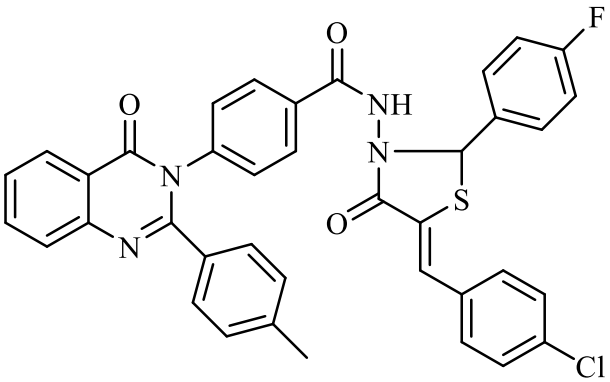
A series of quinazolinone derivatives bearing guanidinopropanoic acid were synthesized, characterized then evaluated for their antimicrobial activity against 11 pathogenic bacteria, 10 pathogenic fungus using ciprofloxacin and Clotrimazole as reference drugs, and it was found that Compound **109** exhibited potent antibacterial and antifungal activity (Figure 58)[96].



109

Figure 58. Structure of compound **109**

Some novel fluorine containing 5-arylidene derivatives bearing different pharmacophores and heterocyclic systems like quinazolinone along with 4-thiazolidinone have been synthesized, were evaluated for their *in vitro* antimicrobial activity against Gram-positive bacteria *(Staphylococcus aureus* and *Streptococcus pyogenes)*, Gram-negative bacteria *(Escherichia coli* and *Pseudomonas aeruginosa)* and fungi *(Candida albicans*, *Aspergillus niger*,and *Aspergillus clavatus)* using serial broth dilution method. Compound **110** was the most active one[97]. Among them compound **110** showed a great activity (Figure 59).

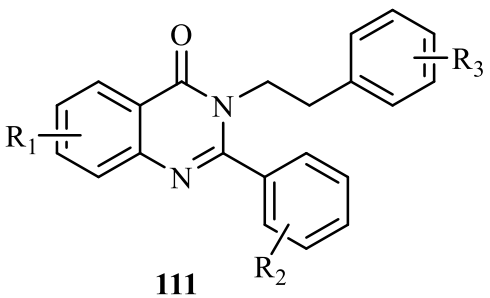


110

Figure 59. Structure of compound **110**

(G) Calcilytic Aactivity

Shcherbakova *et al* synthesized a series of 4(3*H*)-quinazolinones (**111**) that block calcium receptor (calcilytics) leading to stimulation of parathyroid hormone release producing anabolic effects in bone and so, can be used for treatment of osteoporosis (Figure 60)[98].

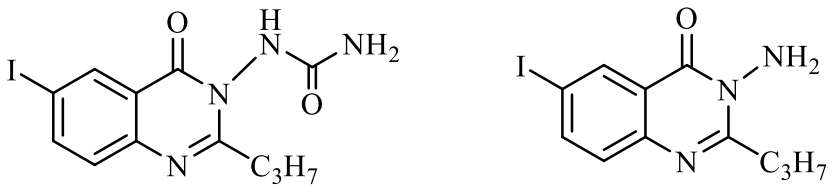


111

Figure 60. Structure of compound **111**

(H) Antioxidant Activity

Al-Omar *et al.* synthesized series of 6-iodo-2-propyl-4(3*H*)-quinazolinone derivatives and these compounds were screened for their antioxidant activity. It was observed that compounds **112** and **113** cause 98% inhibition of aldehydes oxidase (Figure 61)[99].



112 **113**

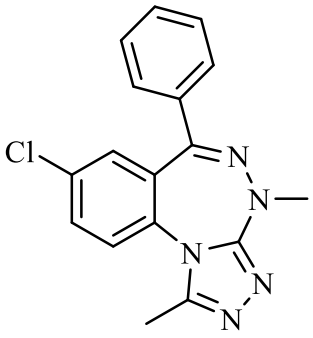
Figure 61. Structure of compounds **112** and **113**

3.2. Biological Activity of Benzotriazepines

Benzotriazepines were found to have various biological activities among of which, C.N.S, anti-cancer, cholecystokinin receptor antagonist and anti-inflammatory activities.

(A) C.N.S Activity

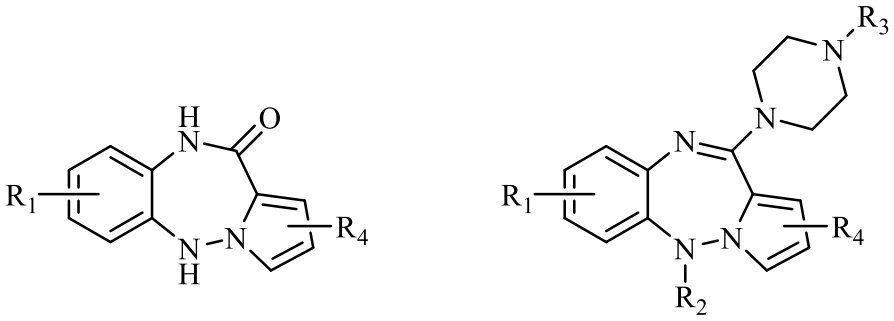
8-Chloro-1,4-dimethyl-6-phenyl-4H-s-triazolo(4,3-a)(1,3,4)benzotriazepine (**114**) was found to have anticonvulsant and antidepressant activities when tested in a mammal. Moreover, it caused100% protection of mice against metrazole induced seizures at a dose level of 60 mg/kg of body weight (Figure 62)[61].



114

Figure 62. Structure of compound **114**

Benzotriazepines (**115**) and (**116**) were prepared and found to act as neuroleptic agents in the treatment of psychotic disturbances such as schizophrenia. Moreover, some derivatives were found to be useful in the treatment of insomnia owing to their antidepressant and sleep-inducing properties (Figure 63)[100].

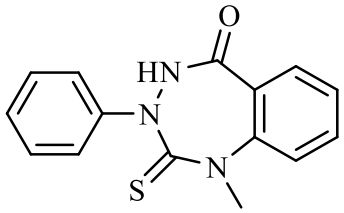


115 **116**

R_1,R_4= H, Halogen, alkyl, alkoxy; R_2= H,alkyl;
R_3= H. alkyl, alkenyl, benzyl.

Figure 63. Structure of compounds **115** and **116** derivatives

A new series of 3,4-dihydro-1H-benzo[e][1,2,4]triazepin-5(2H)-one derivatives were synthesized and evaluated as antipsychotic. It was found that compound **117** had the same antipsychotic activity as reference drug clozapine (Figure 64)[58].

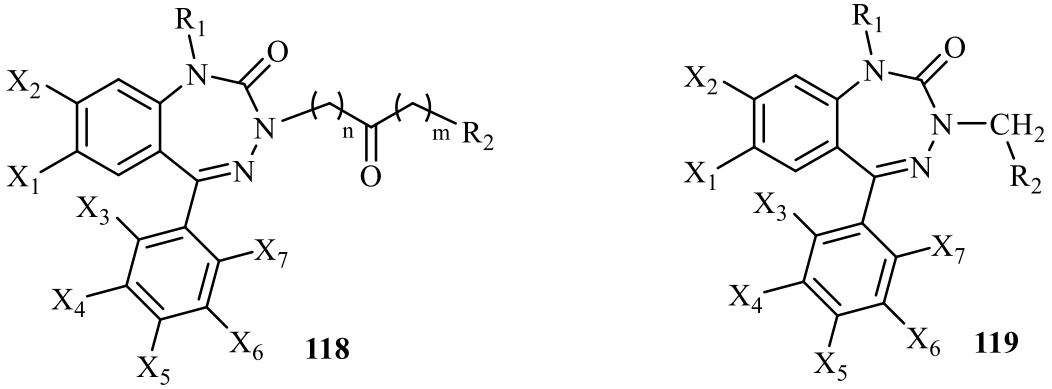


117

Figure 64. Structure of compound **117**

(B) Anti-cancer Activity

Benzotriazepines (**118**) and (**119**) were synthesized and found to be effective against certain forms of cancer, particularly colon cancers, leukemia, and melanoma (Figure 65)[64].

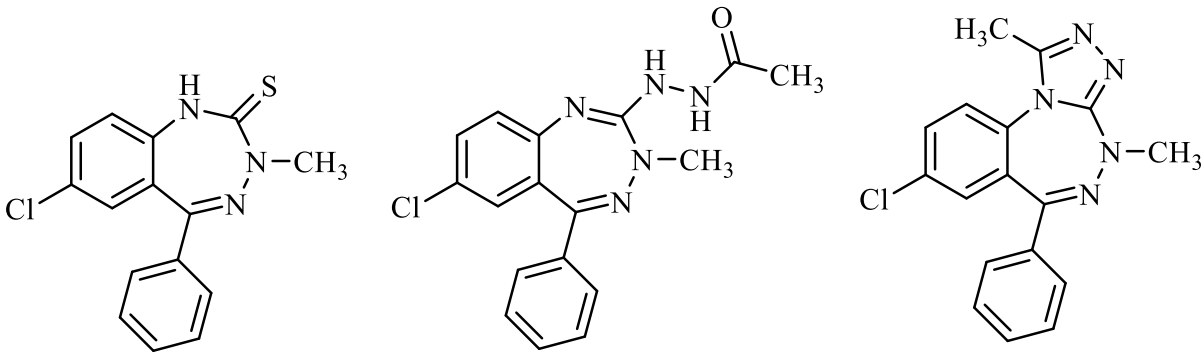


118 **119**

X_{1-7}= H,halogen, C_{1-4} alkyl, hydroxyl, amino;
$R_{1,2}$= H, C_{1-4} alkyl, C_{1-4} alkenyl; n,m= 1,2,3.

Figure 65. Structure of compounds **118** and **119** derivatives

Benzotriazepines (**120**), (**121**) and (**122**) were prepared and found to be potent and highly selective protein interaction inhibitors of bromodomain and extra-terminal (BET) proteins, a family of transcriptional co-regulators that play a key role in cancer cell survival and proliferation (Figure 66)[101].

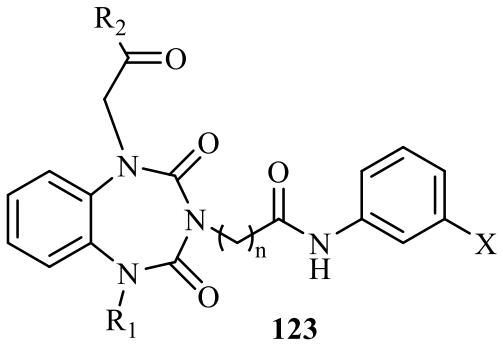


120 **121** **122**

Figure 66. Structure of compounds **120**, **121**, and **122**

(C) Cholecystokinin Receptor Antagonist Activity

A number of CCK_2 antagonists have been reported to play an important role in controlling gastric acid related conditions, nervous system disorders and certain types of cancer[102]. 1H-1,3,5-Benzotriazepine-2,4(3H,5H)-diones (**123**) were prepared and found to bepotent CCK_2 receptor antagonists (Figure 67)[59].



123

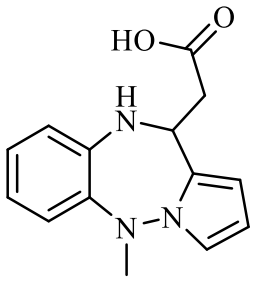
R_1= Ph, c-C_6H_{11}, c-C_7H_{13}; R_2= Pyrrolidin-1-yl,*t*-Bu.

X=H, -CH_3, -NCH_3, -COOH, 1,2,4-oxadiazol-3-yl-5(2H)-one; n-1,2,3.

Figure 67. Structure of compound **123** derivatives

(D) Anti-inflammatory Activity

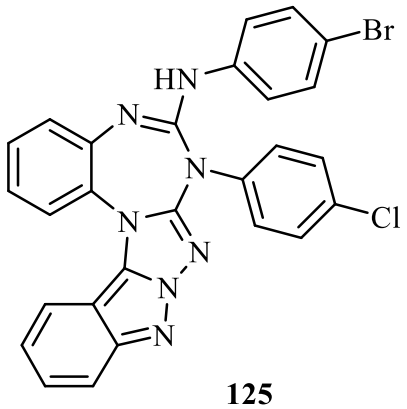
5-Methyl-10,11-dihydro-5H-pyrrolo[1,2-b][1,2,5]benzotriazepin-11-acetic acid (**124**) was prepared and evaluated for its anti-inflammatory activity using the carrageen an-induced rat paw edema method whereas it showed anti-inflammatory effect comparable to that of tolmetin (Figure 68)[103].



124

Figure 68. Structure of compound **124**

Fernandeza P. *et al* synthesized compound **125** and it was found to inhibit cyclooxygenase-2 enzyme (COX-2) leading to anti-inflammatory activity in animal models (Figure 69)[104].



125

Figure 69. Structure of compound **125**

4. Conclusion

The review focused on the preparation and exploration of the biological activities of two important classes of compounds: 4(3*H*)-quinazolinones and benzotriazepines. The first part of the review discussed the preparation of 4(3*H*)-quinazolinone and benzotriazepine derivatives. It provided insights into the synthetic strategies employed to obtain these compounds, highlighting their structural diversity and potential for modification. The second part of the review dealt with diverse biological activities exhibited by 4(3*H*)-quinazolinones. These compounds demonstrated promising effects in various therapeutic fields, including anti-inflammatory activity, antitumor activity, central nervous system activity, cardiovascular system activity, antiviral activity, antimicrobial activity, calcilytic activity, and antioxidant activity. This comprehensive exploration emphasized the potential of 4(3*H*)-quinazolinones as versatile agents in drug discovery and development. Similarly, the review also examined the diverse biological activities of benzotriazepines. These compounds showcased notable effects in central nervous system activity, anti-cancer activity, cholecystokinin receptor antagonist activity, and anti-inflammatory activity. The discussion shed light on the potential applications of benzotriazepines in various therapeutic settings, highlighting their versatility and pharmacological significance. Overall, the findings underscored the importance of these compounds in medicinal chemistry and drug development as reported before in a lot of scientific paperes published before[105-124], emphasizing their potential as promising candidates for the treatment of various diseases. Further research and exploration of these compounds can lead to the development of novel therapeutic agents with enhanced efficacy and reduced side effects.

Authors' contributions

Ahmed S. Abdelkhalek, Mansour E. Abokull, Samy M. Ibrahim, and Mostafa K. Soltan: designed the study, paper preparation, writing original draft, and revised the manuscript. Mokhtar A. Abdul-Malik and Shaban A. A. Abdel-Raheem: revised the manuscript, adjusting the paper linguistically and spelling, and adjusting the paper according to the style of the journal.

Conflict of interest

The authors declare that there is no conflict of interest in the manuscript.

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