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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Sulfa drug analogs: new classes of *N*-sulfonyl aminated azines and their biological and preclinical importance in medicinal chemistry (2000–2018)

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Abstract

N-sulfonylamino azinones has attracted the interest of numerous researchers and extensive investigations on their biological activities have been done. The present review provides an overview of the patents and reports filed during the last few years pertaining to the synthesis *N*-sulfonyl azinones as well as their biological and preclinical studies. A brief discussion on the significant biological findings is also provided. It has been established that *N*-sulfonylamino azinones is privileged heterocycles possessing diuretic, antihypertensive, anti-inflammatory, and anticancer and other biological activities. In particular, a new generation of competitive AMPA receptor antagonist based on *N*-sulfonylamino 1*H*-quinazoline-2,4-diones is promising useful in the treatment neurological disorders such as epilepsy and schizophrenia. The scope of these new advances has been also highlighted in this review.

Keywords Sulfa drug analogs · *N*-sulfonyl aminated azines · Medicinal chemistry · *N*-sulfonyl aminated pyridines · *N*-sulfonyl aminated pyrimidines

Introduction

The sulfonamide moieties are pharmacophore responsible for the biological response of several clinically significant drugs (Scheme 1). Sulfonamides have relieved an increasing interest from organic chemists due to their diverse biological activities, including carbonic anhydrase inhibition (Isik et al. 2009; Al-Rashida et al. 2014), antidiabetic (Riaz et al. 2015), anticancer (Weber et al. 2004; Kamel et al. 2010; Ghorab et al. 2014), antimicrobial (Camoutsis et al. 2010; Nasr et al. 2014; Gadad 2000), and antiviral potencies (Bouissane et al. 2006).

Literature survey revealed that azinones and their benzene derivatives represent important scaffolds in biologically active molecules useful as a potential class of HIV-1 non-nucleoside reverse transcriptase inhibitors (Li et al. 2013; Medina-Franco et al. 2007), as antiproliferative (Hameed et al. 2018), antifungal (Cherif et al. 2015), antibacterial (Hossan et al. 2012; Gezegen et al. 2014), sedative (Collins et al. 2002), and cardiotonic agents (Verrier et al. 2008; Fossa et al. 2003).

In view of the biological significance of azinone scaffolds and sulfonamide pharmacophore, particular focus has been aimed to substitute the nitrogen ring of azinones by amino group of sulfonamide pharmacophores to provide access a novel potentially biological active *N*-sulfonylamino based azinones and their benzene derivatives. Many patents published during the last few years to file the synthesis *N*-sulfonylamino azinones as well as their biological and preclinical studies. Among biological activities of *N*-sulfonylamino azinones that enclosed in the recent available patents, their remarkable promising anti-inflammatory and anticonvulsant potencies was noticed.

Selurampanel, belongs to *N*-sulfonylamino 1*H*-quinazoline-2,4-diones, act as a novel competitive AMPA/kainate receptor antagonist that is being developed by Novartis company. Data obtained from preclinical and small clinical trials referred that Selurampanel is found to have some attractive characteristics such as good oral bioavailability, limited metabolism, no significant affinity for other receptors, good tolerability, and promising efficacy among numerous

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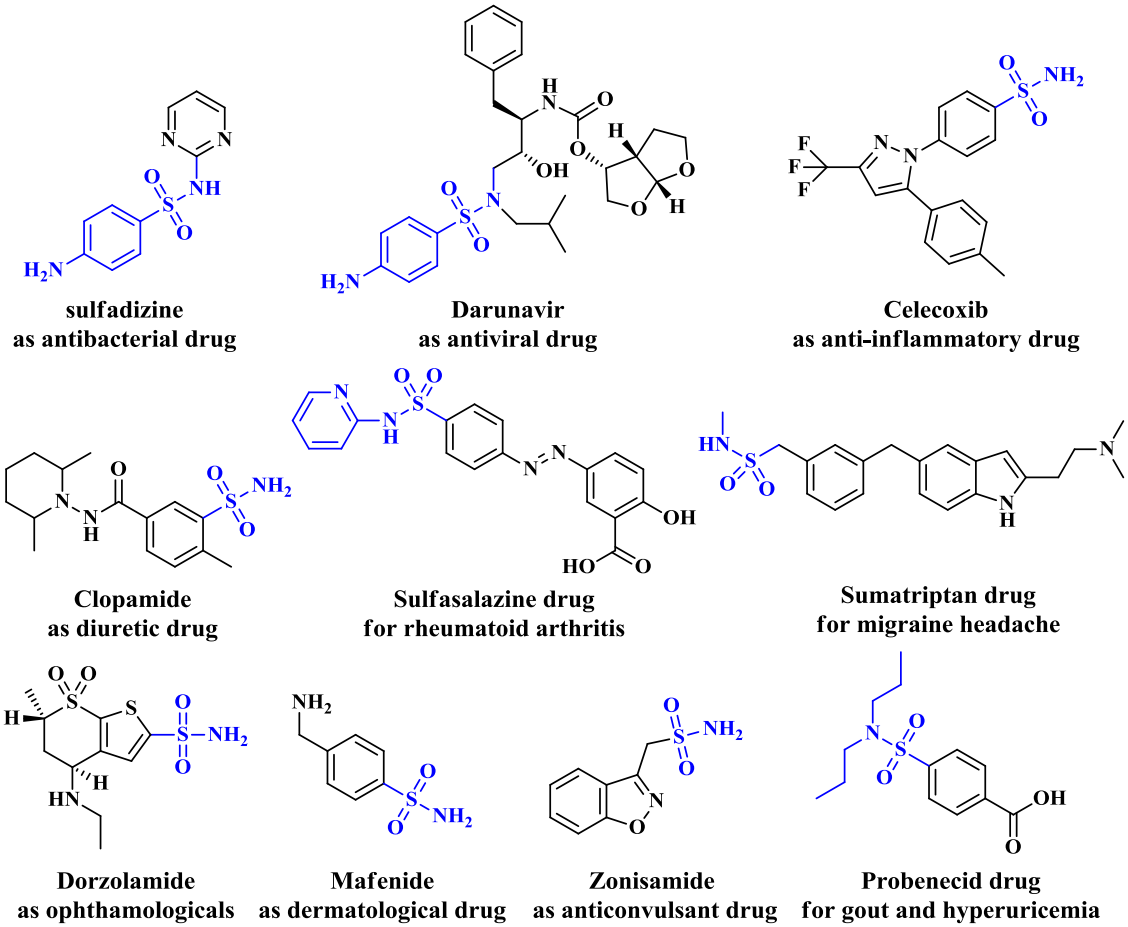


Scheme 1 Representative biologically active sulfonamide-bearing drugs

research subjects (Faught 2014; Hanada 2014; Gomez-Mancilla et al. 2014; Kasteleijn-Nolst Trenité et al. 2015).

Despite of therapeutic potential of *N*-sulfonylamino azinones, the synthesis of this type of sulfonamide analogs are still limited. Nevertheless, considerable research efforts have been done for the synthesis of these rings. Herein, we conducted numerous research investigations for exploring the synthetic routes toward *N*-sulfonylamino azinones and highlighting the most relevant biological results (Scheme 2).

Synthetic methods of *N*-sulfonylamino azinones with their biological investigations

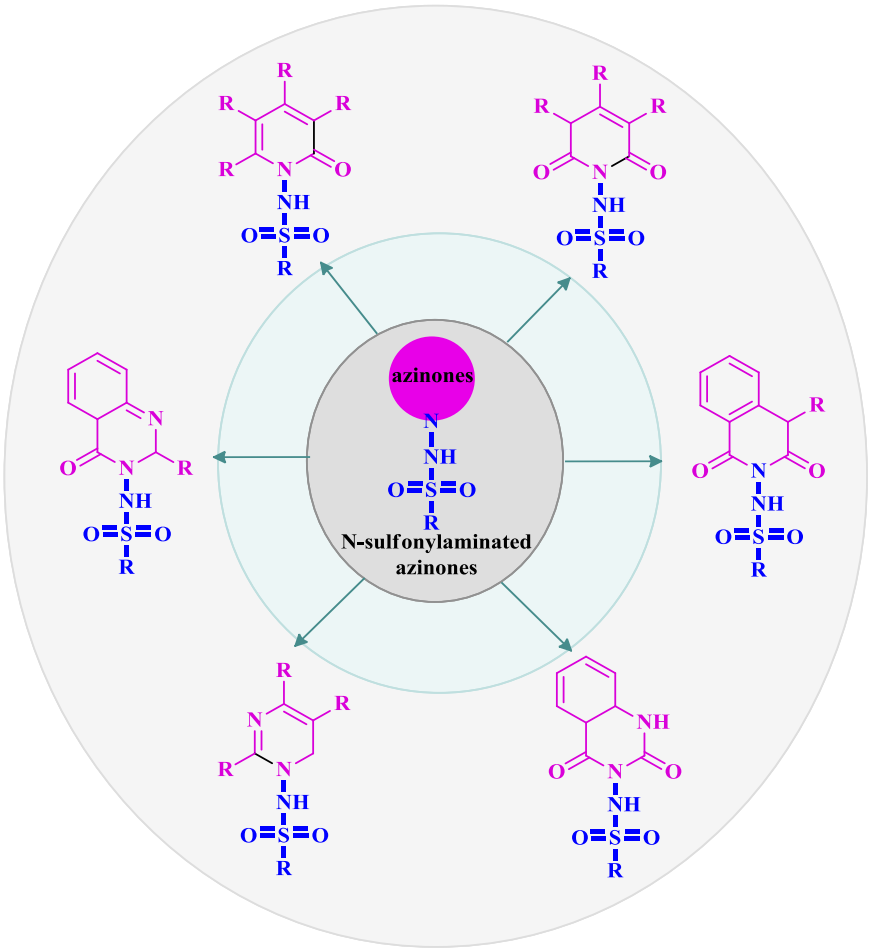
Synthesis of *N*-sulfonylamino azinones containing one hetero atom

Synthesis of *N*-sulfonylamino pyridine-2(1*H*)-one derivatives

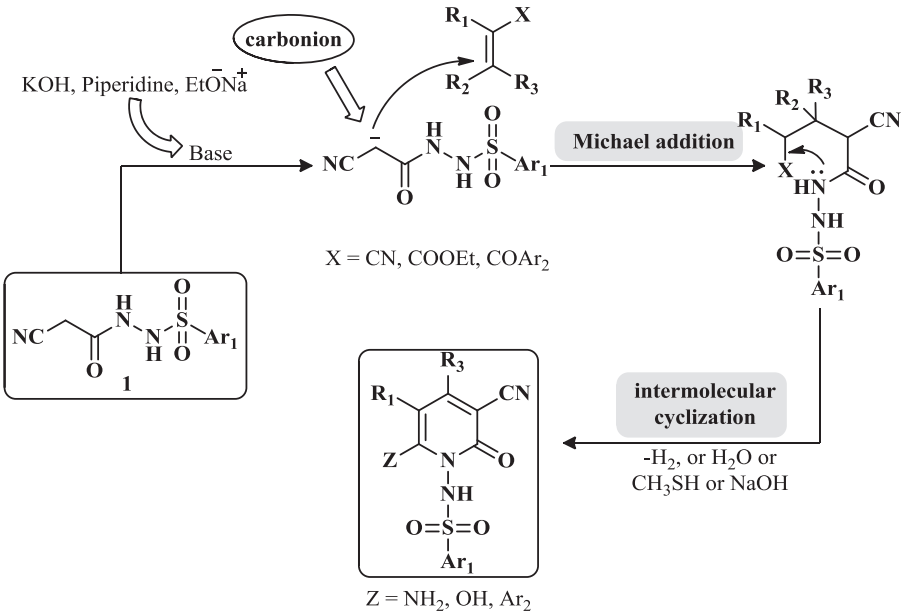
Synthesis of *N*-sulfonylamino pyridine-2(1*H*)-one via Michael addition/intramolecular cyclization sequence Diverse strategies in area of *N*-sulfonylamino 2-pyridones synthesis have been emerged. Among strategies available, Michael addition-intrarmolecular cyclization sequence was extensively reported. The first investigation on the reactivity of *N*-cyanoactoarylsulfonylhydrazides **1** towards various bielectrophiles for the synthesis of *N*-sulfonylamino pyridin-2-ones was described by Elgemeie et al. (1999, 2000, 2001, 2017a, b); Elgemeie and Sayed (2003); Azzam and Elgemeie (2019). A plausible mechanism involved Michael addition of active methylene to the double bond followed by intramolecular cyclization of Michael adduct via nucleophilic attack of nitrogen on carbonyl or cyano groups with loss of small molecule as a shown in Scheme 3.

In the first example, *N*-cyanoactoarylsulfonylhydrazides **1** was subjected to reflux with acrylonitrile derivatives **2** in ethanol in the presence of a catalytic amount of piperdine, leading to *N*-arylsulfonylaminated pyridine-2-one **3**. Interestingly, ethyl arylidenecyanoacetate and arylidene derivatives of benzoylacetonitrile **4** in refluxing pyridine for 6 h, resulting in the formation of ethyl *N*-arylsulfonylamino-2-pyridone-5-carboxylate **5** as the sole product in good yield

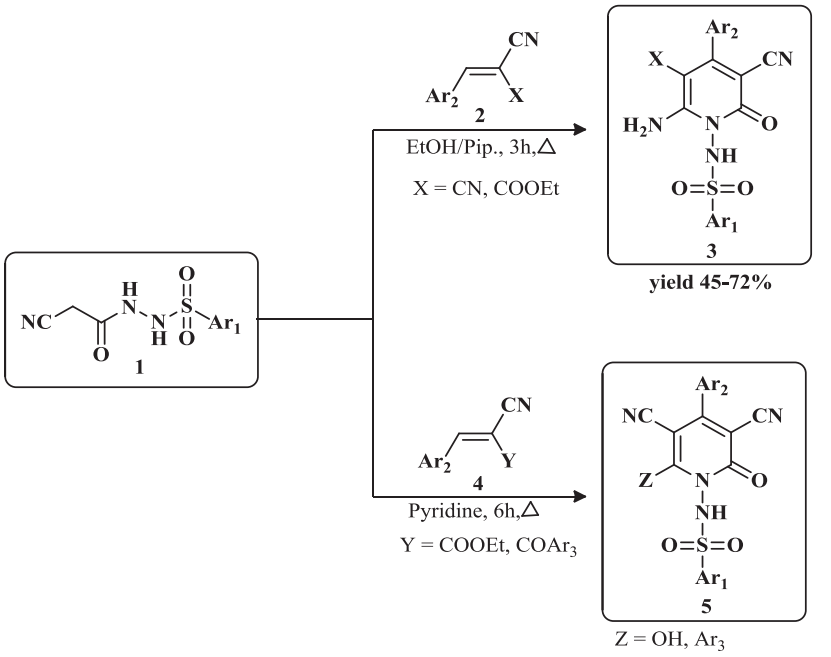
Scheme 2 Some isomeric forms of *N*-sulonylamino azinones



Scheme 3 A plausible mechanism for the reaction of *N*-cyanoacetoarylsulfonylhydrazide with different dielectrophiles

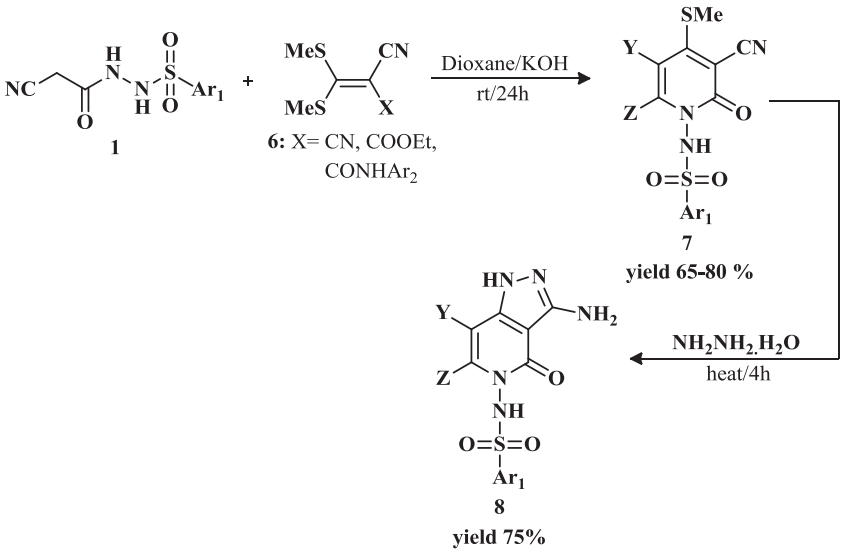


Scheme 4 A synthetic approach for *N*-arylsulfonylamino-2-pyridone derivatives (**3**,**5**)



Ar_1 = C_6H_5, C_6H_4-4-CH_3, Ar_2 = C_6H_5, C_6H_4-4-CH_3, C_6H_4-4-OCH_3, C_6H_4-4-Cl, C_6H_4-4-NO_2, 2-furayl, 2-theinyl, Ar_3 = C_6H_5, C_6H_4-4-CH_3, C_6H_4-4-OCH_3, C_6H_4-4-Cl, C_6H_4-4-NO_2, C_6H_4-4-$N(CH_3)_2$

Scheme 5 Synthetic approaches for 4-methylthio-*N*-arylsulfonylamino-2-pyridones (**7**) and 1*H*-pyrazolo[3,4-*c*] pyridones (**8**)



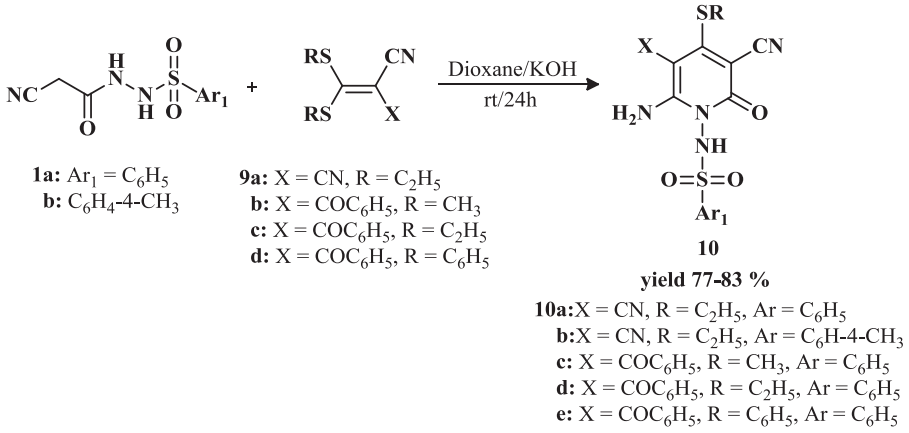
Ar_1 = C_6H_5, C_6H_4-4-CH_3, Z = NH_2, OH, Y = CN, $CONHAr_2$; Ar_2 = C_6H_5, C_6H_4-4-CH_3, C_6H_4-4-OCH_3, C_6H_4-4-Cl

(Scheme 4) (Elgemeie et al. 1999, 2000; Elgemeie and Sayed 2003).

An efficient and facile method was developed for providing direct and easy access to a series of 4-methylthio-*N*-arylsulfonylamino-2-pyridones **7** at room temperature under basic condition using ketene dithioacetals **6** to react with *N*-arylsulfonylhydrazides **1** in dry 1,4 dioxan. The resulting 2-pyridones **7** was then subjected to react with hydrazine hydrate to produced1*H*-pyrazolo[3,4-*c*] pyridones **8** in 65% yield (Scheme 5) (Elgemeie et al. 2001; Azzam et al. 2017).

Very recently, a novel set of 4-alkylthio-*N*-arylsulfonylamino-2-pyridones was synthesized using alternative types of ketene dithioacetals for investigation their antimicrobial potency. The use of 2,2-dicyanoethene-1,1-bis(ethylthiolate) **9a** to undergo intermolecular cyclization with sulfonylhydrazides **1** led to formation of 4-ethylthio-2-pyridones **10a,b** in good yield (Azzam and Elgemeie 2019).

Scheme 6 A synthetic approach 4-alkylthio-*N*-arylsulfonylamino-2-pyridones (**10**)



1a: $Ar_1 = C_6H_5$
b: C_6H_4-4-CH_3

9a: X = CN, R = C_2H_5
b: X = COC_6H_5, R = CH_3
c: X = COC_6H_5, R = C_2H_5
d: X = COC_6H_5, R = C_6H_5

10
yield 77-83 %

10a: X = CN, R = C_2H_5, Ar = C_6H_5
b: X = CN, R = C_2H_5, Ar = C_6H-4-CH_3
c: X = COC_6H_5, R = CH_3, Ar = C_6H_5
d: X = COC_6H_5, R = C_2H_5, Ar = C_6H_5
e: X = COC_6H_5, R = C_6H_5, Ar = C_6H_5

Table 1 Antimicrobial activity of the synthesized compounds **10a**, **b** against a wide range of bacterial and fungal strains

Comp.	Zone of inhibition (mm)					
	Gram (−ve) bacteria				Gram (+ve) bacteria	
	E. coli	*P. aeruginosa*	*S. marcescens*	*S. typhimurium*	*S. aureus*	*B. subtilis*
10a	15.4 ± 0.44	NA	**15.7 ± 0.47**	15.7 ± 0.47	18.2 ± 0.58	17.6 ± 0.58
10b	11.4 ± 0.36	NA	11.4 ± 0.36	11.5 ± 0.43	13.5 ± 0.36	9.8 ± 0.34
CIP	20.6 ± 0.73	23.4 ± 0.61	**19.3 ± 0.42**	24.1 ± 0.51	**30 ± 0.67**	NT
AMP	NT	NT	NT	NT	**27.4 ± 0.72**	32.4 ± 0.67
Comp.	Fungi				Gram (+ve) bacteria	
	C. albicans	*A. fumigatus*	*S. racemosum*	*G. candidum*	*S. pneumoniae*	*E. faecalis*
10a	18.2 ± 0.73	16.3 ± 0.44	18.5 ± 0.58	15.8 ± 0.52	16.7 ± 0.19	15.4 ± 0.38
10b	14.7 ± 0.58	14.9 ± 0.25	8.9 ± 0.31	9.7 ± 0.42	13.3 ± 0.19	11.3 ± 0.39
CIP	NT	NT	NT	NT	24.2 ± 0.86	25 ± 0.72
AMP	NT	NT	NT	NT	24.3 ± 0.86	25.9 ± 0.54
AM	25.4 ± 0.58	23.7 ± 1.2	26.3 ± 0.34	28.7 ± 0.27	NT	NT

CIP ciprofloxacin, *AMP* ampicillin, *AM* amphotericin B are used as reference drugs

NA not activity, *NT* not tested

The bold values for some synthesized compunds indicate remarkable promising biological activites of such compunds as comparising with other synthesized compunds in the same scheme

2-benzoyl-3,3-bis(alkylthio)acrylonitriles **9b–d** was also reported for the synthesis of different 4-alkylthio 2-pyridone analogs **10c–e** (Scheme 6) (Elgemeie et al. 2017a, b).

The results of antimicrobial activity of the synthesized compounds **10a**, **b** against twelve microbial strains showed that compounds **10a**, **b** displayed low potencies against twelve tested organisms as compared to ciprofloxacin and amphotericin B as reference drugs. Notably, these compounds revealed no activity against *Pseudomonas aeruginosa* bacterial strain (Table 1).

On the other hand, antimicrobial activity of the synthesized compounds **10c–e** at concentrations of 1–5 µg/ml was evaluated. It was observed that the titled compounds **10c**, **e** showed no antibacterial activities at concentrations below 4 µg/ml but exhibited more pronounced effects on fungal strain at comparatively lower concentrations. Compound **10e** had more antibacterial potency against *S. aureus* and *E. coli* as compared to compounds **10c**, **e** with zones of growth inhibition of 12 and 18 mm, respectively at 5 µg/ml (Table 2). In this study, SEM analysis was used as evident tool for the effectiveness of the synthesized compounds on the surface of bacterial membrane.

These significant synthetic results prompted Elgemeie and co-workers to react *N*-cyanoactophenylsulfonylhydrazides **1a** with oxime derivatives of *β*-diketones or *β*-ketoesters **11**, producing novel nitroso-2-arylsulfonylamined 2-pyridones **12** as new forms for promising antimetabolite agents (Scheme 7) (Elgemeie and Ali 2003).

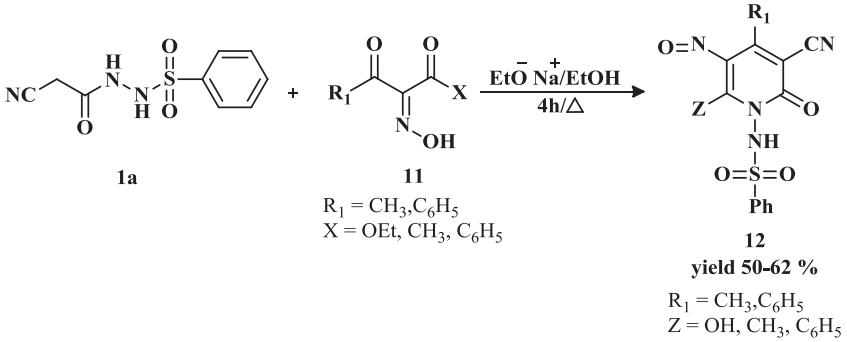
A new synthetic approach for novel non-classical fused pyrid-2-ones **14** was developed using sodium salt of 2-(hydroxymethylene)-1-cycloalkanones **13** as a precursor.

Table 2 Antimicrobial activity of synthesized compounds **10c–e** against *Staphylococcus aureus* (SA), *Escherichia coli* (EC), and *Candida albicans* (CA) using well diffusion test

Comp.	Zone-area inhibition (mm) of synthesized compounds at gradual concentration (mg/mL)[a]														
	1			2			3			4			5		
	EC	SA	CA	EC	SA	CA	EC	SA	CA	EC	SA	CA	EC	SA	CA
10c	–	–	10	–	–	12	–	–	14	0	10	25	11	12	30
10d	–	–	10	–	–	15	–	–	20	10	11	20	12	12	22
10e	–	–	10	–	–	15	10	–	18	15	10	22	18	12	25

[a]For the control antifungal (fluconazole 20 µg), the zone of inhibition was 15 mm, and for the control antibacterial (levofloxacin 3.25 µg), the zone of inhibition was 18 mm

Scheme 7 A synthetic approach for nitroso-2-arylsulfonylamined 2-pyridones (**12**)



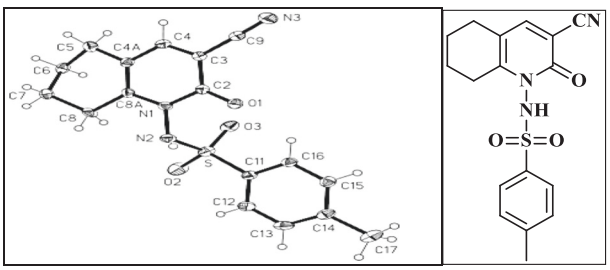


Fig. 1 The X-ray analysis confirmed the exclusive presence of the form **14a** in the solid state

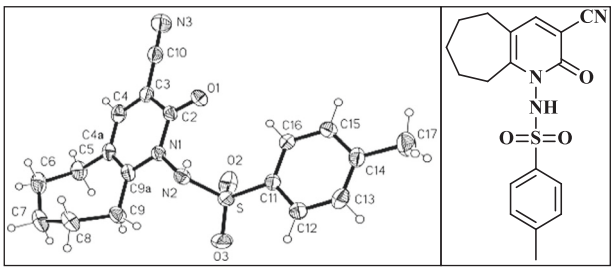


Fig. 2 The X-ray analysis confirmed the exclusive presence of the form **14b** in the solid state

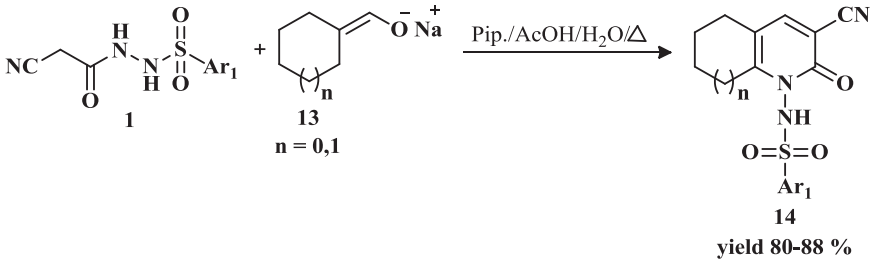
This reaction performed by refluxing *N*-arylsulfonylhydrazides **1** with sodium salt of 2-(hydroxymethylene)-1-cycloalkanones **13** in the presence of piperidine acetate as a catalyst in a mixture of water and ethanol (50:50 vol%) for 10 min followed by addition of acetic acid to hot solution. X-ray analysis was used as sufficiently convincing evidence for production of these fused rings (Figs 1, 2). Notably, this catalytic method has the advantages of short-time reaction and excellent-yielded products (Scheme 8) (Elgemeie and Jones 2002; Elgemeie et al. 2002).

Mohamed (2010) extended this reaction to sodium salt of 3-hydroxy-1-(2-naphthyl)prop-2-en-1-one **15** for synthesis of a new 2-naphtyl-*N*-arylsulfonylamino 2-pyridones **16** in good yield (Scheme 9).

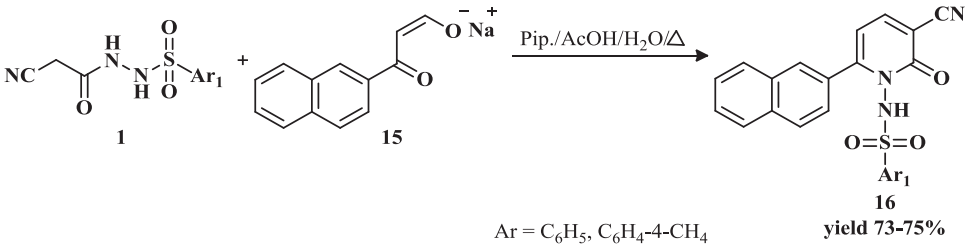
Synthesis of *N*-sulfonylamino pyridine-2(1*H*)-one via sulfonation of *N*-amino pyridine-2(1*H*)-one As a part of discovering new generation of thrombin inhibitors, Bayrakdarian et al. (2005) disclosed in their invention a series of functionalized *N*-sulfonylamino pyridin-2-ones to be useful in treatment thromboembolic disorder. At a first, *N*-amino pyridin-2-one **18** was prepared from 2-methoxy-4-methyl-pyridin-3-acetonitrile via a sequence of acidic hydrolysis, esterification, and transamination. For the synthesis of *N*-sulfonylamino 2-pyridone **19**, *N*-amino pyridine-2-one **18** was sulfonated with different sulfonyl chlorides under basic condition. To provide adequate diversity, analogs featuring various P_3 substituents were synthesized through hydrolysis of ester group in **19**, amide formation, and deprotection cascades (Scheme 10). Authors then demonstrated the data confirming the influence of functionalized *N*-sulfonylamino pyridin-2-ones **20** on thrombin and trypsin activities as a shown in Table 3 (Hassan et al. 2011).

In this series, the pyridin-2-one analogs **20a–p** revealed IC_{50} values against thrombin activity in the range of 0.207 –

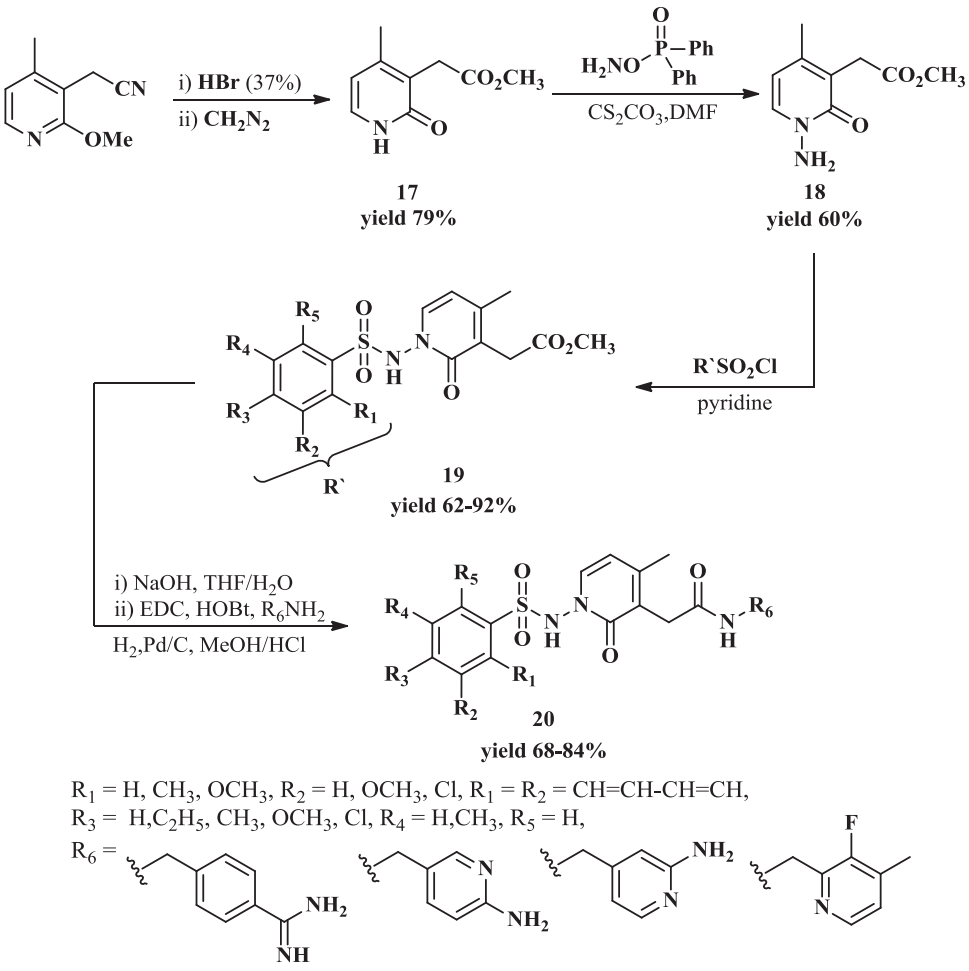
Scheme 8 A synthetic approach for fused pyrid-2-ones (**14**)



Scheme 9 A synthetic approach for 2-naphtyl-*N*-arylsulfonylamino-2-pyridones (**16**)

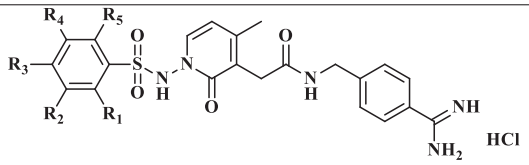


Scheme 10 A synthetic aapproach for *N*-sulfonylamino-2-pyridone analogs with different subunits (**20**)

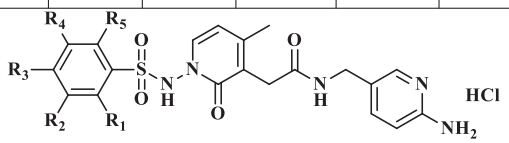


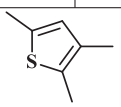
>44.400 μM. Series of the pyridin-2-one analogs containing *N*-(4-carbamimidoyl-benzyl)-2-acetamide subunit **20a–h** displayed significant effect on thrombin and trypsin potencies. The titled compounds **20a–c** exhibited higher activity against thrombin as compared with other synthesized compounds in these set with excellent selectivity over

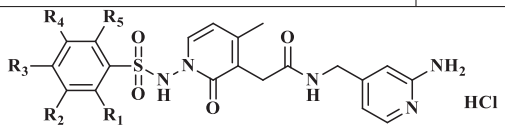
Table 3 IC_{50} values for the synthesized compounds **20a–p** against thrombin and trypsin



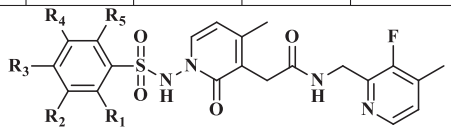
Comp.	R_1	R_2	R_3	R_4	R_5	IC_{50} (μM)		Ratio[a]
						Thrombin	Trypsin	
20a	**OCH_3**	**H**	**Cl**	**H**	**H**	**0.307**	**4.130**	**13**
20b	**CH_3**	**H**	**H**	**CH_3**	**H**	**0.578**	**7.130**	**12**
20c	**H**	**Cl**	**Cl**	**H**	**H**	**0.885**	**10.300**	**12**
20d	H	OCH_3	H	H	H	1.054	15.600	15
20e	OCH_3	H	CH_3	H	H	1.180	2.020	1.7
20f	CH=CH-CH=CH		H	H	H	1.243	17.100	14
20g	H	H	OCH_3	H	H	1.846	3.410	1.8
20h	H	H	H	H	H	2.471	5.770	2.3



Comp.	R_1	R_2	R_3	R_4	R_5	IC_{50} (μM)		Ratio[a]
						Thrombin	Trypsin	
20j								
20k	OCH_3	H	OCH_3	H	H	>44.400	>44.400	-
20l						>44.400	>4.400	-



Comp.	R_1	R_2	R_3	R_4	R_5	IC_{50} (μM)		Ratio[a]
						Thrombin	Trypsin	
20m	H	H	C_2H_5	H	H	>44.400	>44.400	-



Comp.	R_1	R_2	R_3	R_4	R_5	IC_{50} (μM)		Ratio[a]
						Thrombin	Trypsin	
20n	CH_3	H	H	H	Cl	>44.400	>44.400	-
20o	SO_2CH_3	H	H	H	H	>44.400	>44.400	-
20p	CH_3-CH_2-CH_2-CH_3					>44.400	>44.400	-

[a]Ratio of (IC_{50} trypsin)/(IC_{50} thrombin)

The bold values for some synthesized compunds indicate remarkable promising biological activites of such compunds as comparising with other synthesized compunds in the same scheme

trypsin. Compound **20a** was found to be potential thrombin inhibitor with IC_{50} 0.307 μM.

Faidallah et al. (2011) synthesized *N*-sulfonylamino 2-pyridones **23a**, **b** for evaluation their antimicrobial activities but the results revealed that none of the tested compounds exhibited significant antimicrobial activity. An attempt to enhance antibacterial activities, the same group introduced hydrazono moiety to 2-pyridone ring at P_3. After investigation the effect of this moiety on potency of a range of pathogens, appreciable results were shown. The titled compound **23d** showed moderate to good antibacterial activity against the tested antimicrobial strains Additionally, this compound exhibited higher potency against all tested pathogenic bacteria specially *Staphylococcus aureus* than compound **23c** (Table 4). Concerning the synthesis of these compounds, 1-amino-2*H*-pyridin-2-ones derived from pyran-2-one **21** was sulfonated with various sulfonyl chlorides in pyridine under refluxing (Scheme 11) (Faidallah et al. 2013).

Table 4 In vitro antimicrobial activity of the synthesized compounds **23c**, **d**

Comp.	*S. aureus*		*B. subtilis*		*E. coli*		*P. aeruginosa*		*C. albicans*	
	IZ[a]	MIC[b]	IZ	MIC	IZ	MIC	IZ	MIC	IZ	MIC
23c	18	100	16	200	10	–	NA	–	8	–
23d	20	15	18	50	14	200	10	–	16	100
AMP.	36	12.5	30	25	32	25	27	50	NT	NT
CTM.	–	–	–	–	–	–	–	–	42	12.5

Standard drugs: ampicillin trihydrate (AMP) and clotrimazole (CTM)

[a]Inhibition zone (mm)

[b]Minimal inhibitory concentration (μg/mL)

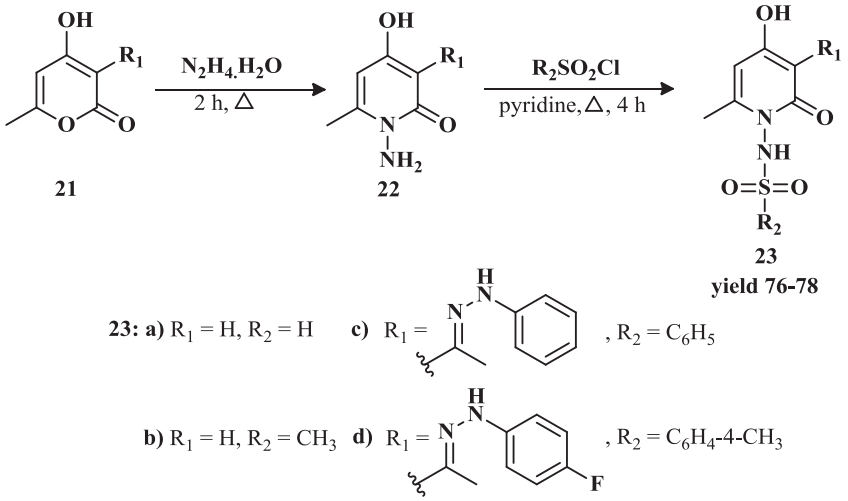
– not tested

Synthesis of *N*-sulfonylamino pyridine-2,6(1*H*,3*H*)-dione derivatives

In recent years, there has been growing interest in chlorophyll-related compounds with a six-membered imide ring due to their good spectra and photophysical properties. These features make them promising as photosensitizers in photodynamic therapy for diseases such as cancer. From this point, Mironov et al. 2003a, b successfully synthesized six-membered *N*-sulfonylamino cycloimide of bacteriochlorin **27**. Addition of hydrazine hydrate to a solution of purpurin **24** in pyridine opened anhydride ring and produced a mixture of isomeric monohydrazides **25a**, **b** and **25c**, **d**. *N*-aminocycloimide **26** was obtained via intramolecular cyclization of monohydrazides in acidic medium followed by esterification of carboxylic group. Sulfonation of **26** with tosyl chloride afforded the desired cycloimides **27** in excellent yield (Scheme 12).

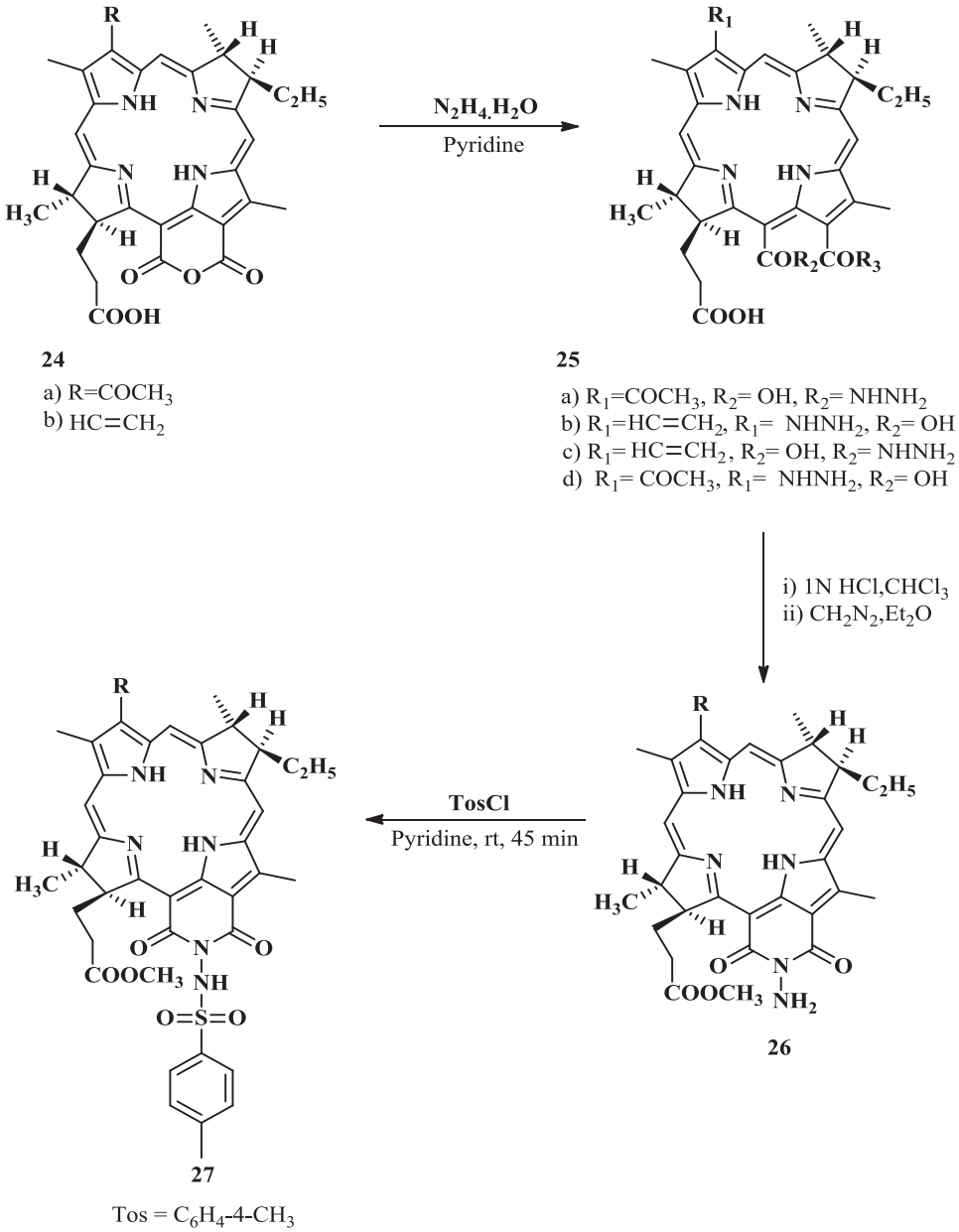
Synthesis of *N*-sulfonylamino isoquioline-1,3(2*H*,4*H*)-diones

An one pot and efficient protocol for the synthesis of *N*-sulfonylamino 2,4-dihydroisoquioline-1,3(2*H*,4*H*)-diones **29** was reported by Kumar et al. (2015). Microwave-assisted condensation of 4-alkyl benzenesulfonohydrazide **28** with isochroman-1,3-dione provided access to 3,4-dihydroisoquinolin-1,3-dione **29** in high yield. The synthesized compounds **29a**, **b** were evaluated their in vitro anticancer activity against different human cancer cell lines, including breast (T47D), colon (HCT-15), lung (NCl H-522), liver (Hep G2), and ovary (PA-1) (Scheme 13).

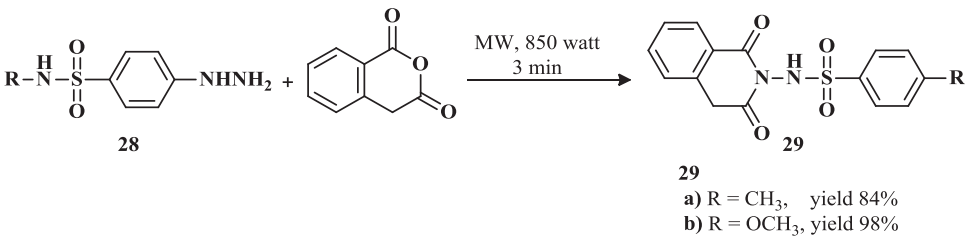


Scheme 11 A synthetic approach for 4-hydroxy-6-metyl 3-substituted *N*-sulfonylamino-2-pyridones (**23**)

Scheme 12 A synthetic approach for *N*-sulfonylamino cycloimides of bacteriochlorin (**27**)



Scheme 13 A synthetic approach for *N*-sulfonylamino 2,4-dihydroisoquioline-1,3 (2*H*,4*H*)-diones (**29**)



The results of in vitro anticancer study revealed that the synthesized compound **29a** possessed higher growth inhibition % against liver Hep G2 and lung NCl H-522 at a concentration of 10^{-5} M than that of standard drugs i.e., 5-fluorouracil, cyclophosphamide, and cycloheximide (Table 5).

Table 5 In vitro anticancer activity of the synthesized *N*-sulfonylamino isoquiolin-1,3-diones **29a**, **b** against five cancer cell lines

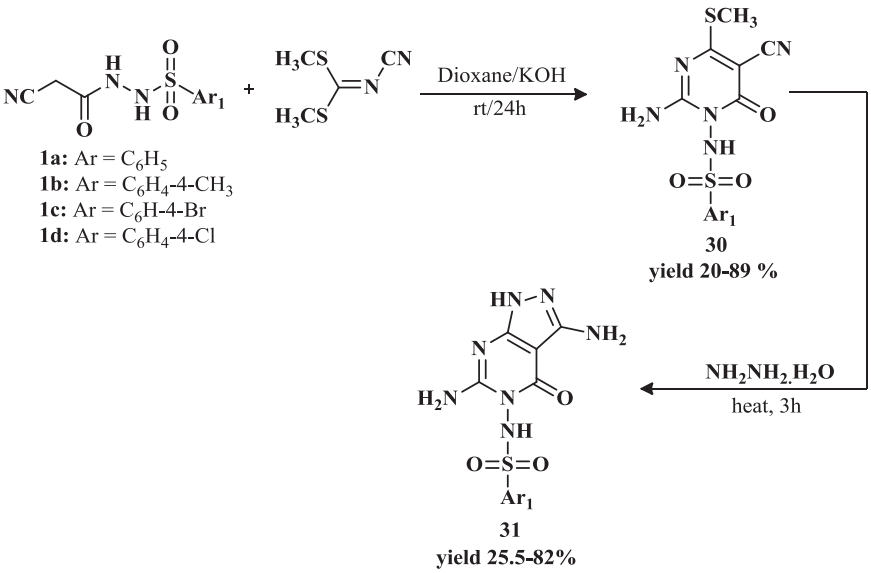
Comp.	Anticancer activity (growth inhibition %) at a concentration of 1×10^{-5} M				
	Lung (NCI H-522)	Liver (Hep G2)	Breast (T47D)	Colon (HCT-15)	Ovary (PA-1)
29a	**41**	**34**	**03**	**20**	**04**
29b	03	18	00	0	13
5-FU[a]	26	19	19	22	20
CYC-PHO[b]	13	20	26	11	15
CYC-HEXI[c]	15	19	17	14	32

[a]5-FU: 5-fluorouracil

[b]CYC-PHO: cyclophosphamide

[c]CYC-HEXI: cycloheximide

Scheme 14 Synthetic approaches for *N*-sulfonylamino methylthiopyrimidin-2-ones (**30**) and 1*H*-pyrazolo[3,4-*d*] pyrimidines (**31**)



Synthesis of *N*-sulfonylamino sulfonylamino azinones containing two hetero atom

Synthesis of *N*-sulfonylamino pyrimidin-4(3*H*)-one derivatives

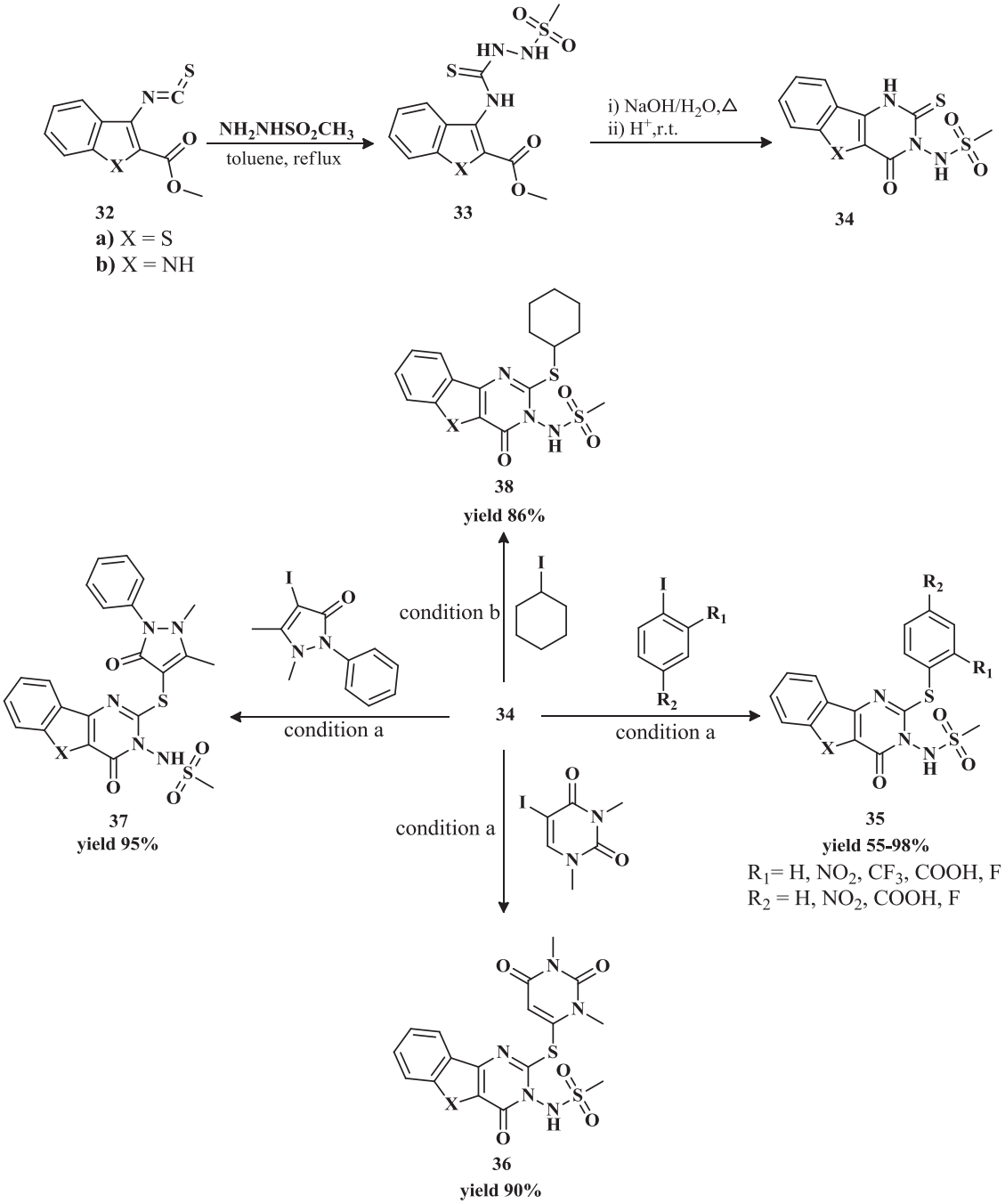
The first synthesis of *N*-sulfonylamino methylthiopyrimidin-2-ones **30** as non-nucleoside analogs was reported by Elgemeie et al. (2017a, b), Elgemeie and Sood (2006), Azzam et al. (2019), who represented the reaction of *N*-cyanoactoarylsulfonylhydrazides **1** with dimethyl *N*-cyanodithioiminocarbonate in the presence of potassium carbonate to provide easy access of *N*-sulfonylamino methylthiopyrimidin-2-ones **30** in low to excellent yield. 1*H*-pyrazolo[3,4-*d*]pyrimidines **31** was also prepared via treatment of pyrimidin-2-ones **30** with hydrazine hydrate (Scheme 14).

In comparison with standard drugs, compound **30c** exhibited high potency against all tested bacterial and fungal strains except *Aspergillus flavus* fungus. In contrast, compound **30d** showed no activity against all aforementioned strains. These findings indicated the effect of bromo substituent on benzene ring of sulfonamide moiety on antibacterial potency (Table 6).

A series of thieno[3,2-*d*]pyrimidin-4-ones was developed by Barone et al. (2013, 2014) as a novel class of anti-inflammatory agents. In this synthetic approach, isothiocyanate derivative **32a** was subjected to reflux with methanesulfonohydrazide to afford methylsulfonylthiosemicarbazide **33a** which underwent to intramolecular cyclization to give thieno[3,2-*d*]pyrimidin-4-one **34a** in 40% yield. Thieno[3,2-*d*]pyrimidin-4-one **34a** was then used as precursor in the synthesis of the corresponding benzothioaryl derivatives **35**–**38a**. The reaction of thieno[3,2-*d*] pyrimidin-4-one **34a** with a variety of aryl and heterocyclic iodides in a mixture of water and ethanol under basic condition in the presence of catalytic amount of copper powder and copper iodide for 6 h furnished benzo-thioaryl

Table 6 Antibacterial and antifungal data of the synthesized compounds **30c**, **d**

Inhibition zone diameter (mm)						
Comp.	*B. subtilis*	*E. coli*	*P. aeruginosa*	*S. aureus*	*A. flavus*	*C. albicans*
30c	**15**	**15**	**13**	**15**	**0**	**15**
30d	0	0	0	0	0	0
Standard drugs	20	22	17	18	17	19



Scheme 15 A synthetic approach for novel thieno[3,2-*d*]pyrimidin-4-one derivatives (**35**–**38**)

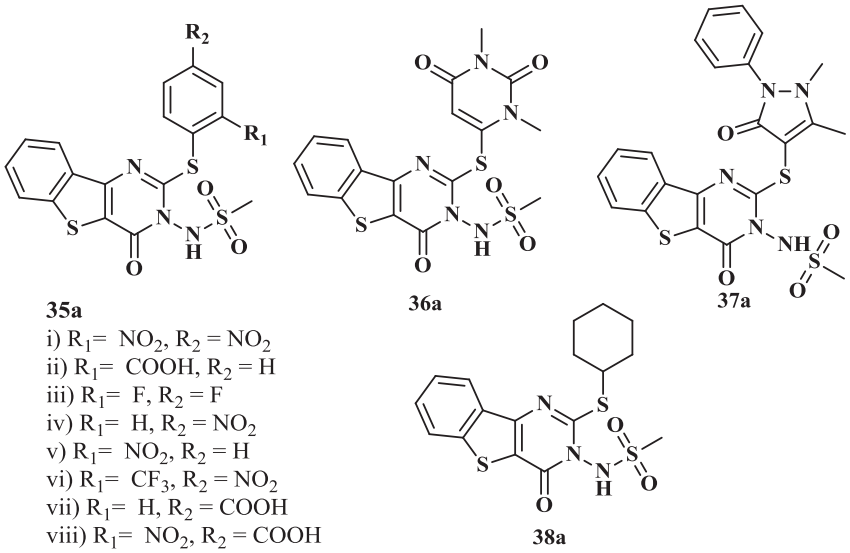
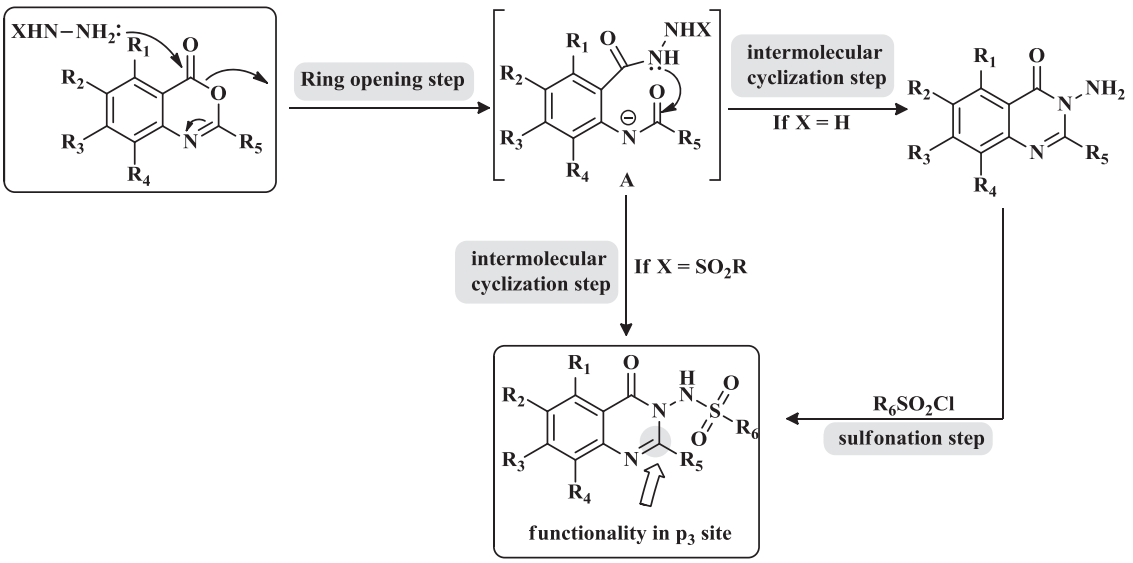


Fig. 3 The most active compounds **35ai-vii**, **36a, 37a, 38a** against iNOS and COX-2 of normal human keratinocytes (NCTC 2544) and mouse monocyte-macrophages (J774)

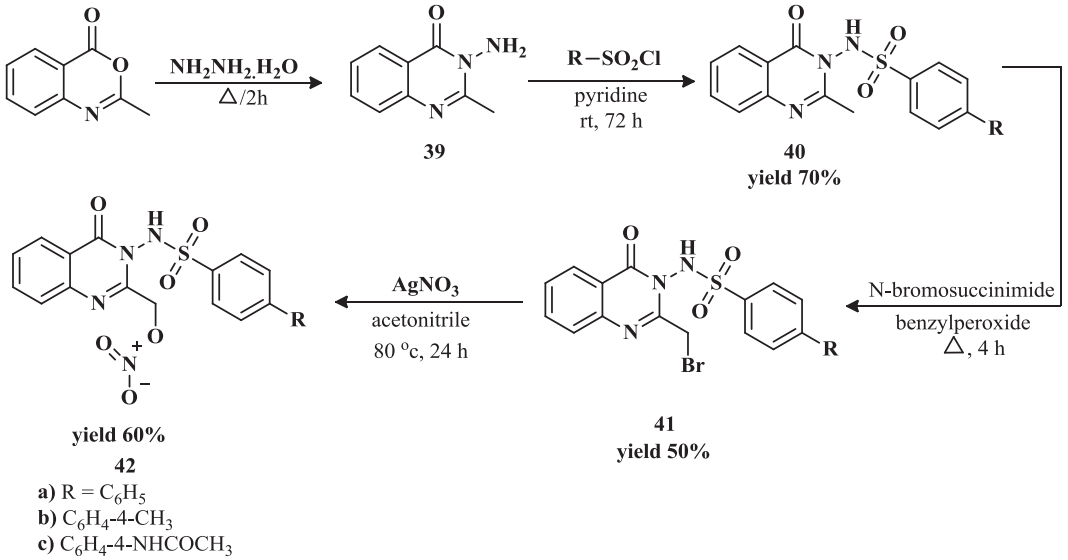
Table 7 iNOS and COX-2 IC_{50} values (μM) of human keratinocytes (NCTC 2544) and mouse monocyte-macrophages (J774) treated with interferon-γplus histamine and lipopolysaccharides

IC_{50} (μg/mL)									
Comp.	NCTC2544		J774		Comp.	NCTC2544		J774	
	iNOS	COX-2	Inos	COX-2		iNOS	COX-2	iNOS	COX-2
35ai	**8 ± 0.3**	**8 ± 1**	**7.8 ± 0.9**	**8.2 ± 0.4**	**35avii**	22 ± 2	25 ± 3	23 ± 0.5	25 ± 1
35aii	**6.5 ± 1.3**	**6.2 ± 0.8**	**6.5 ± 1.5**	**6.2 ± 0.5**	**35aviii**	34 ± 2	35 ± 0.5	31 ± 2	34 ± 0.9
35iii	**5.8 ± 0.3**	**6.1 ± 1.5**	**6.5 ± 0.9**	**6.2 ± 0.6**	**36a**	**7 ± 0.9**	**6.7 ± 0.3**	**6.5 ± 0.5**	**6.9 ± 0.5**
35aiv	35 ± 0.5	32 ± 2	33 ± 0.8	35 ± 1	**37a**	**5 ± 0.2**	**4.5 ± 0.5**	**4.8 ± 0.3**	**5 ± 0.1**
35av	38 ± 2	36 ± 0.9	35 ± 3	37 ± 2	**38a**	**7 ± 0.2**	**6.8 ± 0.5**	**7.3 ± 0.3**	**6.9 ± 0.9**
35avi	32 ± 3	31 ± 2	29 ± 3	33 ± 0.9					

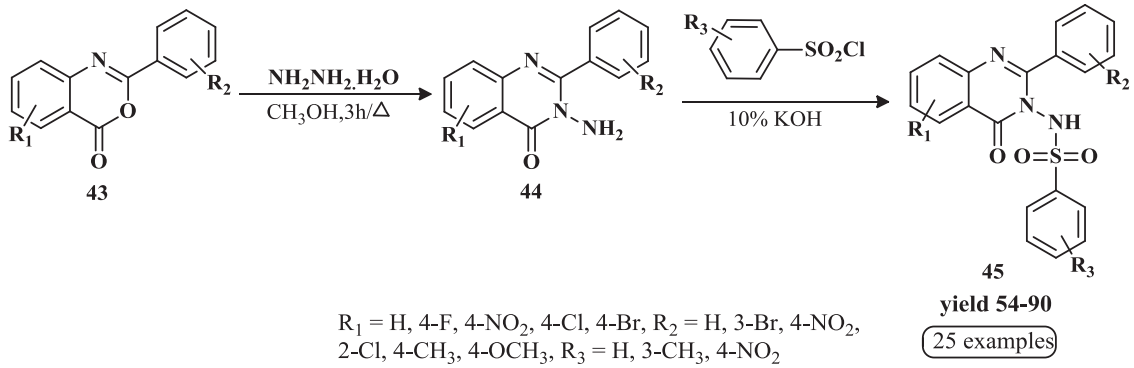
The bold values for some synthesized compunds indicate remarkable promising biological activites of such compunds as comparising with other synthesized compunds in the same scheme



Scheme 16 Synthetic pathways for *N*-sulfonylamino quinazolin-4(3*H*)-ones using benzoxazin-4-ones as precursors



Scheme 17 A synthetic appproach for quinazolin-4(3*H*)-ones containing nitric oxide release moiety (**42**)



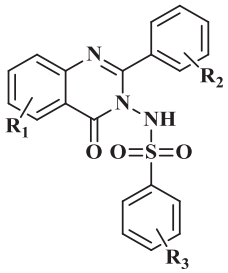
Scheme 18 A synthetic approach for diverse functionalized *N*-sulfonylamino quinazolin-4-one analogs (**45**)

Table 8 Data of the in vitro COX-1/COX-2 inhibition assay and in vitro cyclooxygenase inhibition assay

Comp.	% Edema inhibition	IC_{50} (μM)		IS
		COX-2	COX-1	
40a	77.25	8.58 ± 0.85	30.13 ± 1.49	3.50
40b	83.89	5.75 ± 1.63	32.66 ± 8.46	5.67
40c	95.73	4.41 ± 0.50	22.76 ± 4.60	5.16
42a	54.98	42.10 ± 1.96	98.63 ± 5.48	2.41
42b	71.56	11.66 ± 1.55	38.83 ± 10.87	3.32
42c	>100	3.59 ± 0.24	24.13 ± 3.70	6.72
Meloxicam	100	1.37 ± 0.30	19.40 ± 0.40	14.16

derivatives **35**–**37a** in good yield. The benzo-thio-cycloesyl derivative **38** was obtained from the reaction of thieno[3,2-*d*]pyrimidin-4-one **34a** with cyclohexyl iodide in the presence of potassium carbonate in dimethylformamide at 80 °C (Scheme 15) (Barone et al. 2013). In 2014, The same group was also synthesized new 3,5-dihydro-4*H*-pyrimido [5,4-*b*]indol-4-one derivatives **35**–**38b** in the similar manner (Scheme 15) (Barone and Catalfo 2014; Barone et al. 2014).

Among this series, the titled compounds **35ai–vii**, **36a, 37a, 38a** possessed lower IC_{50} values in a range of 4.5–7.3 μg/mL against iNOS and COX-2 of normal human keratinocytes (NCTC 2544) and mouse monocyte-macrophages (J774) than the other synthesized compounds (Fig. 3). Also, These displayed more interesting anti-inflammatory properties compared to celecoxib as anti-inflammatory drug, expressed by their capacity for counteracting some proinflammatory effects induced via IFN-γ plus histamine in human keratinocyte cells as well as LPS in monocytemacrophage at concentration of 10 μM at concentration of 10 μM (Table 7).



45

a) R_1 = 4-F, R_2 = 3-Br, R_3 = H
b) R_1 = 4-F, R_2 = 2-Cl, R_3 = H
c) R_1 = 4-NO_2, R_2 = H, R_3 = CH_3
d) R_1 = 4-NO_2, R_2 = 4-OCH_3, R_3 = 4-CH_3
e) R_1 = 4-Br, R_2 = 3-Br, R_3 = 4-NO_2
f) R_1 = 4-Cl, R_2 = 4-OCH_3, R_3 = 4-NO_2

Fig. 4 The synthesized compounds **45a–f** as potential diuretic and antihypertensive agents

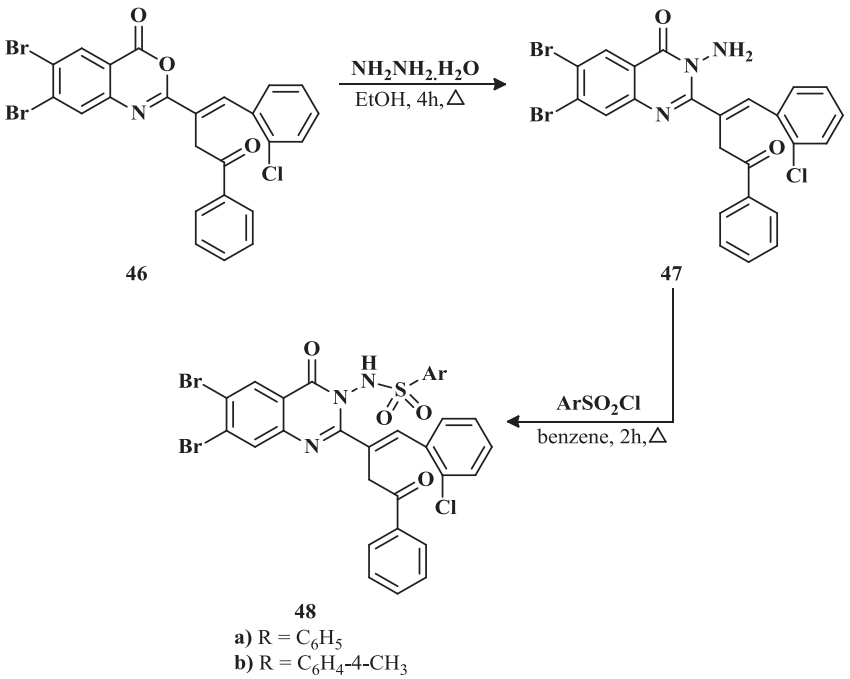
Table 10 Antitumor activity of the synthesized compounds **48a**, **b** against brain tumor cell line (U251) and liver tumer cell line (Hepg)

Comp.	IC_{50} (μg/mL)	
	Brain tumor cell line (U251)	Liver tumor cell line (Hepg)
48a	4.83	9.54
48b	2.14	9.00
DOX	0.7	0.8

Table 9 Diuretic and antihypertensive activities of the most potent synthesized compounds **45a–f** and the changing in blood glucose concentration after 38 h treatment time

Comp.	Diuretic activity data			Antihypertensive activity data		The effect on insulin secretion	
	Total urinary output (mL)	Normal saline intake	Diuretic action	%RSBP	%RMAP	Blood glucose concentration (mg/dL)	
						0 h	48 h
45a	6.49 ± 0.013	4.02 ± 0.148	1.12	18.55	36.16	87.0 ± 1.207	89.6 ± 0.974
45b	6.30 ± 0.016	4.20 ± 0.169	1.09	19.07	36.66	86.3 ± 0.785	91.3 ± 0.811
45c	6.77 ± 0.022	4.19 ± 0.269	1.17	18.55	36.16	90.1 ± 1.024	91.0 ± 0.749
45d	7.18 ± 0.019	4.90 ± 0.138	1.24	19.58	38.08	92.3 ± 0.688	89.7 ± 0.912
45e	8.19 ± 0.019	4.70 ± 0.322	1.42	20.61	39.83	87.4 ± 0.993	91.0 ± 0.759
45f	**9.18 ± 0.022**	**4.73 ± 0.149**	**1.59**	**23.71**	**46.25**	**85.6 ± 1.763**	**91.7 ± 0.915**
Metolazone	9.15 ± 0.175	5.02 ± 0.234	1.59				
Diazoxide				23.19	44.66	86.9 ± 2.058	121.0 ± 0.706
Control						90.7 ± 0.610	91.1 ± 0.785

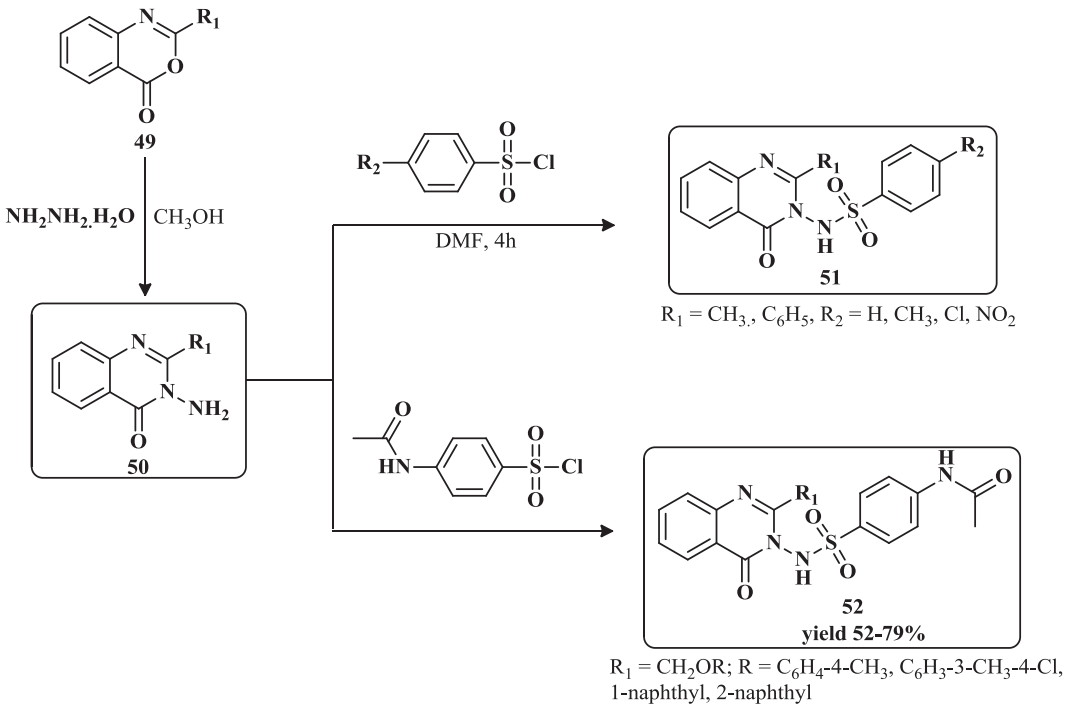
Scheme 19 A synthetic approach for the *N*-sulfonylamino quniazolin-4-ones (**48**)



46 **47**

48

a) R = C_6H_5
b) R = C_6H_4-4-CH_3



Scheme 20 A synthetic approach for 2,3-disubstituted 4(3*H*)quinazolinone derivatives (**52**, **53**)

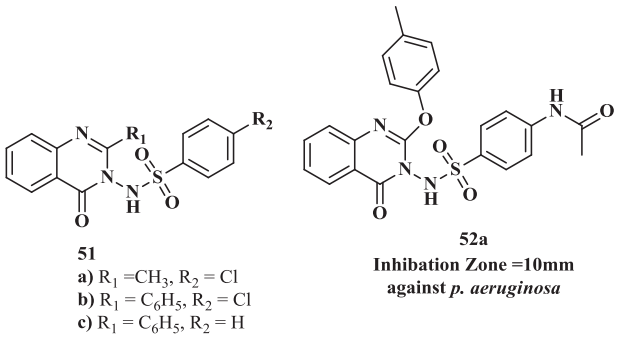


Fig. 5 The most potent compounds **51a–c**, **52a** against wide range of bacterial strains

Synthesis of N-sulfonylamino quinazolin-4(3*H*)-ones

Synthesis of *N*-sulfonylamino quinazolin-4(3*H*)-ones using benzoxazin-4-ones as precursors Two main synthetic routes are available toward *N*-sulfonylamino quinazolin-4(3*H*)-ones from benzoxazin-4-ones. The first route consists of three steps: ring opening of benzoxazin-4-one ring, intermolecular cyclization, and sulfonation as a shown in Scheme 16. The second route provides convergent access to *N*-sulfonylamino quinazolin-4(3*H*)-ones. This route based on ring opening of benzoxazin-4-one ring following by intermolecular cyclization benzamide **A**. A great interest has been put to exploring the biological activities of *N*-sulfonylamino quinazolin-4(3*H*)-one derivatives core motif incorporating varied functionality in p3 site.

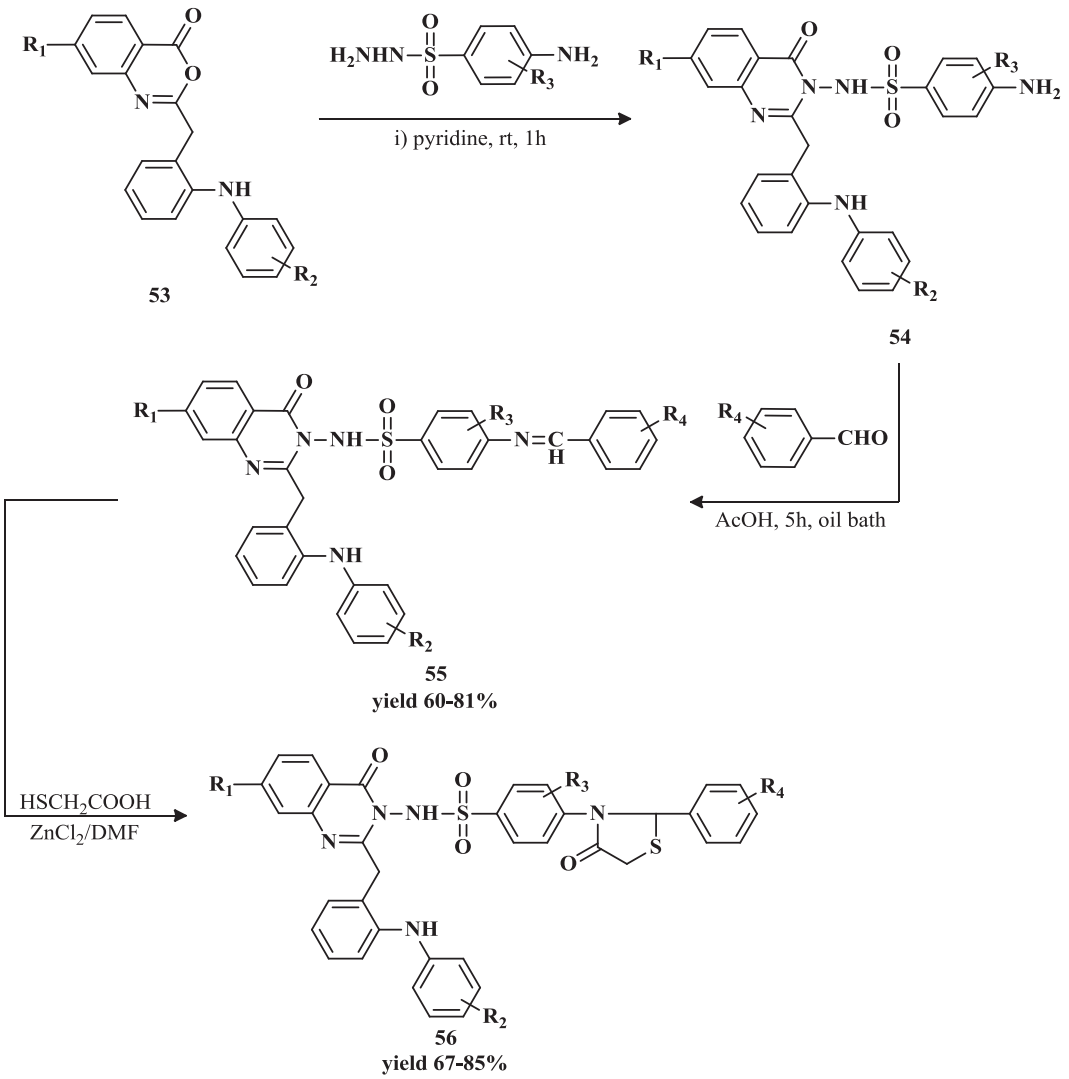
Synthesis of *N*-sulfonylamino quinazolin-4(3*H*)-ones via ring opening/intramolecular cyclization/sulfonation sequence Farag et al. (2015) reported a novel quinazolin-4(3*H*)-ones derivatives containing nitric oxide release moiety at p_3 site as preferential COX-2 inhibitors. 3-methyl benzoxazin-4-one was firstly heated with hydrazine hydrate to afford *N*-amino quinazolin-4(3*H*)-ones **39** which subsequently sulfonated with different sulfonyl hydrazide to give *N*-amino quinazolin-4-ones **40**. For preparation of quinazolin-4(3*H*)-one derivatives with nitric oxide release moiety **42** as hybrid molecule, benzoyl peroxide-catalyzed bromination of **40** with *N*-bromosuccinimide generated bromomethyl derivatives **41** which then reacted with silver nitrate in dry acronitrile (Scheme 17).

Anti-inflammatory activity of the synthesized quinazolin-4-ones **40**, **42** was examined on carrageenan induced rat paw edema and compared the results with meloxicam as a reference standard of 100% potency after 3 h of treatment in a dose 80 mg/kg. In vivo anti-inflammatory test confirmed that all tested compounds revealed significant difference from carrageenan group except compound **42a**. The titled compound **42c** exhibited higher potency than reference drug meloxicam. Additionally, in vitro cyclooxygenase inhibition assay showed that compound **42c** possessed lower IC_{50} value ($IC_{50} = 3.59\ \mu M$) than that of other tested compounds.

Table 11 Antibacterial activity of the most active synthesized compounds **51a–c**

Comp.	Zone of inhibition (mm)						
	B. subtilis	*P. aeruginosa*	*K. pneumonia*	*S. pneumonia*	*E. coli*	*S. aureus*	*P. fluorescence*
51a	+++	+++	+++	+++	++	+++	+++
51b	++	+	+	+++	++	+++	+
51c	+++	++	+++	+++	++++	+++	++

+ indicates very week activity, ++ indicates week activity, +++ indicates moderate activity, ++++ indicates good activity



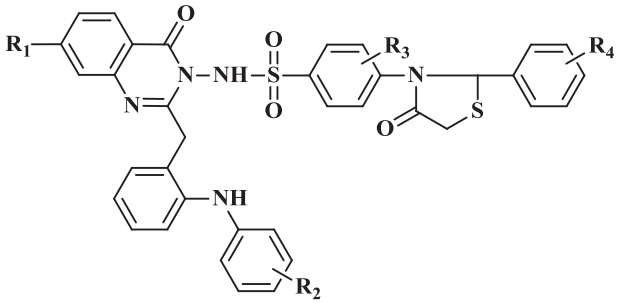
R_1 = H, 4-Cl, 4-Br, R_2 = R_3 = H, 3,5-Cl, R_4 = 2-Cl, 4-Cl, 2-OH, 4-OH, 2-NO_2, 3-NO_2, 4-OCH_3, 3,4,5-(OCH_3),2-OH-4-N(C_2H_5)$_2$, 2-OH-4-OCH_3, 3-OCH_3-4-OH, 4-N(CH_3)$_2$, 4-N(C_2H_5)$_2$

Scheme 21 A synthetic approach for thiazolidinyl quinazolin-4-ones (**56**)

However, Meloxicam standard drug showed lower IC_{50} value (IC_{50} = 1.37 µM) as compared to compound **42c** (Table 8).

Rahman et al. (2014) designed a series of quinazolin-4-one derivatives **45** to be useful as diuretic and anti-hypertensive agents. Diverse functionalized benzoxazin-4-one derivatives **43** was utilized as precursors in the synthesis of *N*-amino quinazolin-4-ones **44**, which could easily sulfonated with various aryl sulfonyl chlorides to result in a wide range of *N*-sulfonylamino quinazolin-4-one derivatives **45** in moderate to excellent yield (Scheme 18).

Remarkable results were obtained from diuretic and antihypertensive activity data. Six compounds **45a–f** exhibited excellent cumulative urine output in this series as compared with standard drug metolazone (Fig. 4). Diuretic action of compound **45f** showed 1.25 times more active than metolazone at a double dose. In comparison with standard drugs prazosin and diazoxide, compounds **45a–f** revealed good reduction in mean arterial blood pressure systolic blood pressure (%RSBP) and mean arterial blood pressure (%RMAP), while compound **45f** showed significant antihypertensive activities at a dose of 5 mg/kg. After evaluation anti-diabetic potential of compounds **45a–f**, no significant fall or increase in the normal glucose level was observed, but diazoxide revealed significant increase in the level of normal glucose (Table 9).



56

a) R_1 = H, R_2 = 3,4-Cl, R_3 = H, R_4 = 2-OH-4-N(C_2H_5)$_2$
b) R_1 = Br, R_2 = 3,4-Cl, R_3 = 3,4-Cl, R_4 = 4-OCH
c) R_1 = Cl, R_2 = 3,4-Cl, R_3 = H, R_4 = 4-Cl
d) R_1 = H, R_2 = 3,4-Cl, R_3 = 3,4-Cl, R_4 = 2-NO_2
e) R_1 = Cl, R_2 = 3,4-Cl, R_3 = H, R_4 = 2-Cl

Fig. 6 The synthesized compounds **56a–e** with low minimum inhibitory concentration against different pathogenic microbe

For more interesting biologically active of *N*-sulfonylamino quniazolin-4-ones, Abdel-Rahman (2006) investigated the efficacy of a new bulky *N*-sulfonylamino quniazolin-4-ones **48** on brain (U251) and liver (Hepg 2) carcinoma cell lines. It was observed that the synthesized compounds possessed lower IC_{50} values against brain (U251) than that of liver (Hepg 2). By comparing with Doxorubicin anticancer drug, compounds **48a**, **b** displayed remarkable effect on brain tumor cell line (U251) with IC_{50} values less than 5 µg/mL (Table 10). With regard to their synthesis, the static benzoxazin-4-ones **46** could facilely convert to *N*-amino quniazolin-4-one **47** under heating with hydrazine hydrate and subsequently sulfonated the resulting *N*-amino quniazolin-4-one **48** with different sulfonyl chlorides (Scheme 19).

Padithem et al. (2013) employed benzoxazin-4-ones **49** to react with hydrazine hydrate for providing access to *N*-amino quniazolin-4-ones **51**, which then sulfonated with

Table 12 The minimum inhibitory concentration (MIC) of the most potent compounds **56a–e**

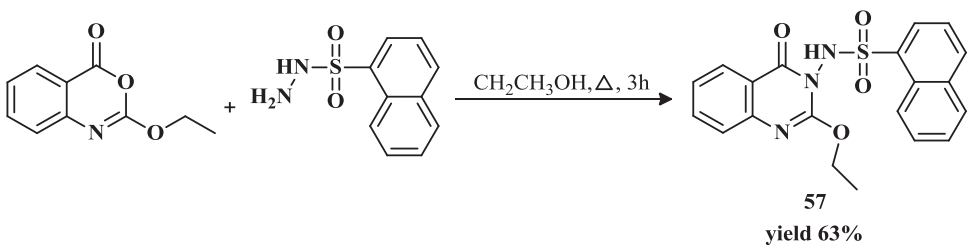
MIC (µg/Ml)							
Comp.	Gram (−ve) bacteria		Gram (−ve) bacteria		Fungi		
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*	*A. clavatus*
56a	**62.5**	100	**62.5**	125	1000	1000	1000
56b	**62.5**	**62.5**	250	250	1000	1000	1000
56c	**50**	250	125	200	**200**	250	500
56d	**50**	125	250	**62.5**	1000	1000	1000
56e	500	500	**62.5**	125	**500**	250	500
A[a]	250	100	100	100	–	–	–
G[b]	–	–	–	–	500	100	100

[a]Ampicillin

[b]Griseofulvin as standard drugs

The bold values for some synthesized compunds indicate remarkable promising biological activites of such compunds as comparising with other synthesized compunds in the same scheme

Scheme 22 A synthetic approach for *N*-(2-ethoxy-4-oxoquinazolin-3(4*H*)-yl) naphthalene-1-sulfonamide (**57**)



57
yield 63%

different sulfonyl chlorides (Scheme 20). The resulting *N*-sulfonylamino quniazolines **51** was evaluated their antibacterial activity against seven bacterial strains. In vitro antibacterial results indicated that *N*-sulfonylamino quniazolin-4-ones **51a–c** had higher potency than other synthesized compounds (Fig. 5). Quantum mechanical calculations were correlated with the results of antibacterial test (Table 11). El-Moghazy et al. (2012) used benzoxazin-4-ones bearing ester group at p_2 **49** to obtain more static *N*-sulfonylamino quniazolin-2-one **52** in similar synthetic manner. The synthesized compounds **52** were also examined their antibacterial activity. However, these compounds showed no activity against all the tested bacteria strains except compound **52a** showing low activity against *P. aeruginosa* with inhibition zone 10 mm (Scheme 20).

Synthesis of *N*-sulfonylamino quniazoline via ring opening / intramolecular cyclization sequence Patel et al. (2010a, b, c, d) devoted considerable efforts to discover chemically diverse novel thiazolidinyl quinazolin-4-ones **56** as antimicrobial agents. At a first, *N*-sulfonylamino quniazolin-4-ones **54** were easily prepared after stirring for 1 h after addition of 4-aminoarylsulfonyl hydrazide to a cold solution of benzoxazinones **53** in pyridine. The acid-catalyzed condensation of **54** with substituted aromatic aldehydes gave schiff bases **55**, which could react with thioglycolic acid in the presence of a pinch of $ZnCl_2$ to afford the desired thiazolidinyl quinazolin-4-ones **56** (Scheme 21).

The results obtained from broth micro dilution method indicated that some of 4-thiazolidinone derivatives **56a–e** exhibited promising antibacterial activity whereas pronounced antifungal potency was observed (Fig. 6). The titled compounds **56a–d** exhibited lower minimum inhibition concentration against *E. coli* as compared with Ampicillin. Both of compounds **56a**, **b** showed good bacterial activity against *S. aureus* with MIC value 62.5 µg/ml. Compound **56d** was only compound possessed lower MIC value against *S. pyogenus* than other tested compounds as well as Ampicillin (Table 12).

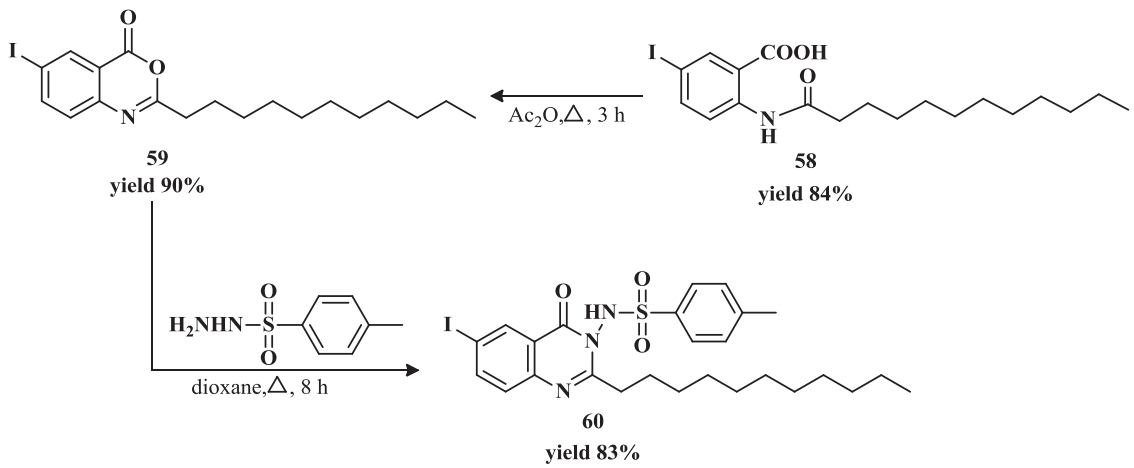
El-Hashash et al. (2011) studied the behavior of 2-ethoxy-(4*H*)-3,1-benzoxazin-4-one toward nitrogen nucleophiles, including the steric *o*-naphthalenesulonyl hydrazide. In this study, 2-ethoxy-(4*H*)-3,1-benzoxazin-4-one was subjected to react with the steric *o*-naphthalenesulonyl hydrazide in boiling ethanol to furnish a novel quinazolin-2-one derivative **57** (Scheme 22).

After evaluation the antimicrobial activity of quniazolin-2-one **57**, it was found that compound **57** was antibacterially active and comparatively efficient. Also, this compound exhibited good antifungal potency against *A. flavus* and *C. albicans* strains as compared with Amphotericin B (Table 13).

Very recently, Hekal and Abu El-Azm (2018) prepared a new dynamic 6-iodo-2-undecyl benzoxazinone **59** derived from 2-amino-5-iodobenzoic acid to use as a precursor in the synthesis of *N*-sulfonylamino 2-undecylquinazolin-4(3*H*)-one **60**. The latter was facilely produced via treatment **59** with 4-methylbenzenesulfonohydrazide in a yield of 85% (Scheme 23). Authors evaluated the anticancer activity of the newly *N*-sulfonylamino 2-undecylquinazolin-4(3*H*)-one **60**.

Table 13 In vivo antimicrobial activity by agar diffusion method of the tested compound **57**

Comp.	Inhibition zone diameter (mm/mg sample)			
	E. coli	*S. aureus*	*A. flavus*	*C. albicans*
57	16	16	12	15
Tetracycline	33	31	–	–
Amphotericin B	–	–	17	21



Scheme 23 A synthetic approach for the newly *N*-sulfonylamino 2-undecylquinazolin-4(3*H*)-one (**60**)

The synthesized compound **60** exhibited relatively good potency towards hepatocellular carcinoma (HePG-2) with an IC_{50} value of 16.73 ± 1.4 µg/ml as compared with doxorubicin (IC_{50} = 4.50 ± 0.2) but showed moderate activity against colon cancer (HCT-116) as well as mammary gland breast cancer (MCF-7) (Table 14).

A developed method for the synthesis of 3-substituted quinazolin-4-one derivatives **61** was reported via melting of benzoxazinones **49** with several sulfonyl hydrazides under solvent free conditions at 130 °C but this method was not recommended on a larger scale (>0.2 mmol). This attributed with the potential uncontrollable decomposition of substituted sulfonyl hydrazides. 3-Substituted quinazolin-4-one **61** was produced in low to excellent yield with traces of benzamides **62** (Scheme 24) (Zhou et al. 2004).

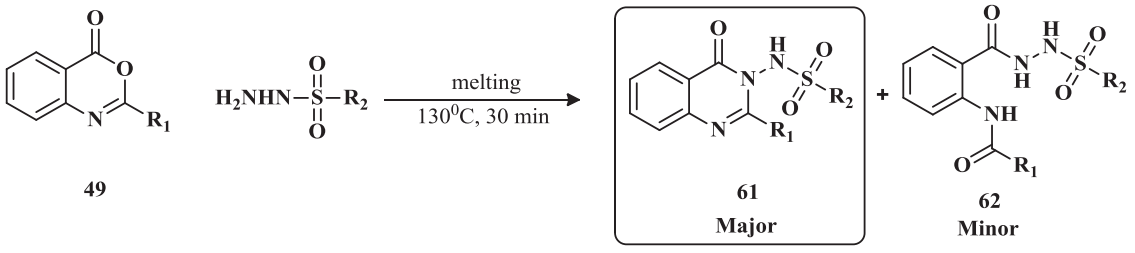
For sticking more convergent method for the synthesis of 3-substituted quinazolin-4-ones from benzoxazinones, Jagani et al. (2011) introduced microwave radiation to prepare 3-substituted quinazolin-2-one **65** in good yield instead into classical conditions. All quinazolin-2-one derivatives **65** were synthesized utilizing 1.3 equivalents of *N*-(4-(hydrazinylsulfonyl)phenyl)acetamide in the presence of 0.2 equivalent of pyridine as a base in DMF under microwave irradiation. Acid catalyzed-hydrolysis of quinazolinones **64** was achieved to yield (*E*)-4-amino-*N*-(4-oxo-2-substituted styrylquinazolin-3(4*H*)-yl)benzenesulfonamide **65** using microwave irradiation at 140 W (Scheme 25).

Synthesis of *N*-sulfonylamino quinazolin-4(3*H*)-ones using 2-acetamidobenzoic acids as precursors An efficient protocol was developed for *N*-sulfonylamino quinazolin-4(3*H*)-ones via microwave-assisted the reaction of 2-acetamidobenzoic acid derivatives **66** with N-(4-(hydrazinylsulfonyl)phenyl)acetamide in presence of a stoichiometric amount of PCl_3. 3-substituted quinazolin-4-one **67** was converted to (*E*)-4-amino-*N*-(4-oxo-2-substituted alkylquinazolin-3(4*H*)-yl)benzenesulfonamide **68** as discussed above in Jagani report (Jagani et al. 2011). 4-(3*H*) Quinazolinone **68** efficiently could undergo diazotization-coupling to afford the corresponding hydrazono derivatives **69**. A series of biological active pyrazole substituted quinazolinones **71** were obtained by treatment of pyrazono derivatives **69** with hydrazine hydrate under microwave irradiation and evaluated their antibacterial activity (Scheme 26) (Sojitra et al. 2016). In continuation, the same group investigated rhodanine to participate as coupling agent in diazotization-coupling reaction for the synthesis of a novel rhodanine substituted quinazolinone derivatives **70** (Scheme 26) (Sojitra et al. 2013).

In general, all tested compounds **70** and **71** revealed more selectivity against gram negative over gram positive bacterial strains. Quinazolin-4(3*H*)-ones containing the group 4-chlorophenyl substitution at the 2nd position **70a–c** showed lower minimum inhibition valves (MIC) than other tested quinazolin-4(3*H*)-ones, Methaqualone and Sulfanilamide drugs but possessed higher MIC values than

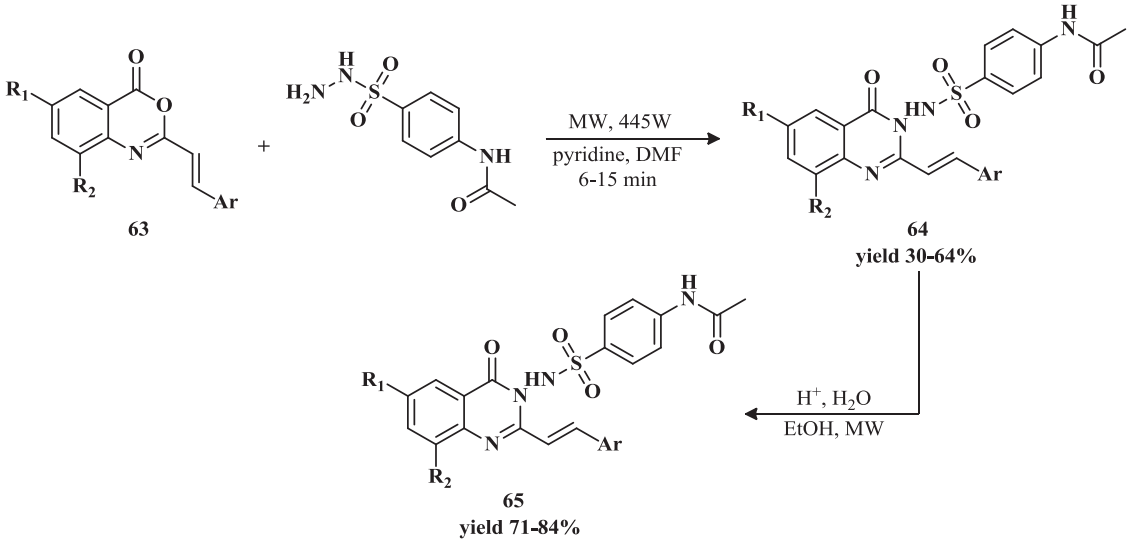
Table 14 Cytotoxicity (IC_{50}) of the tested compound **60** on different cell lines (HepG2, HCT-116, MCF-7)

Comp.	IC_{50} (µg/mL)		
	Hepatocellular carcinoma cell line (HePG2)	Colon cancer cell line (HCT-116)	Mammary gland breast cancer cell line (MCF-7)
60	16.73 ± 1.4	21.87 ± 1.7	39.50 ± 2.7
DOX	4.50 ± 0.2	5.23 ± 0.3	4.17 ± 0.2



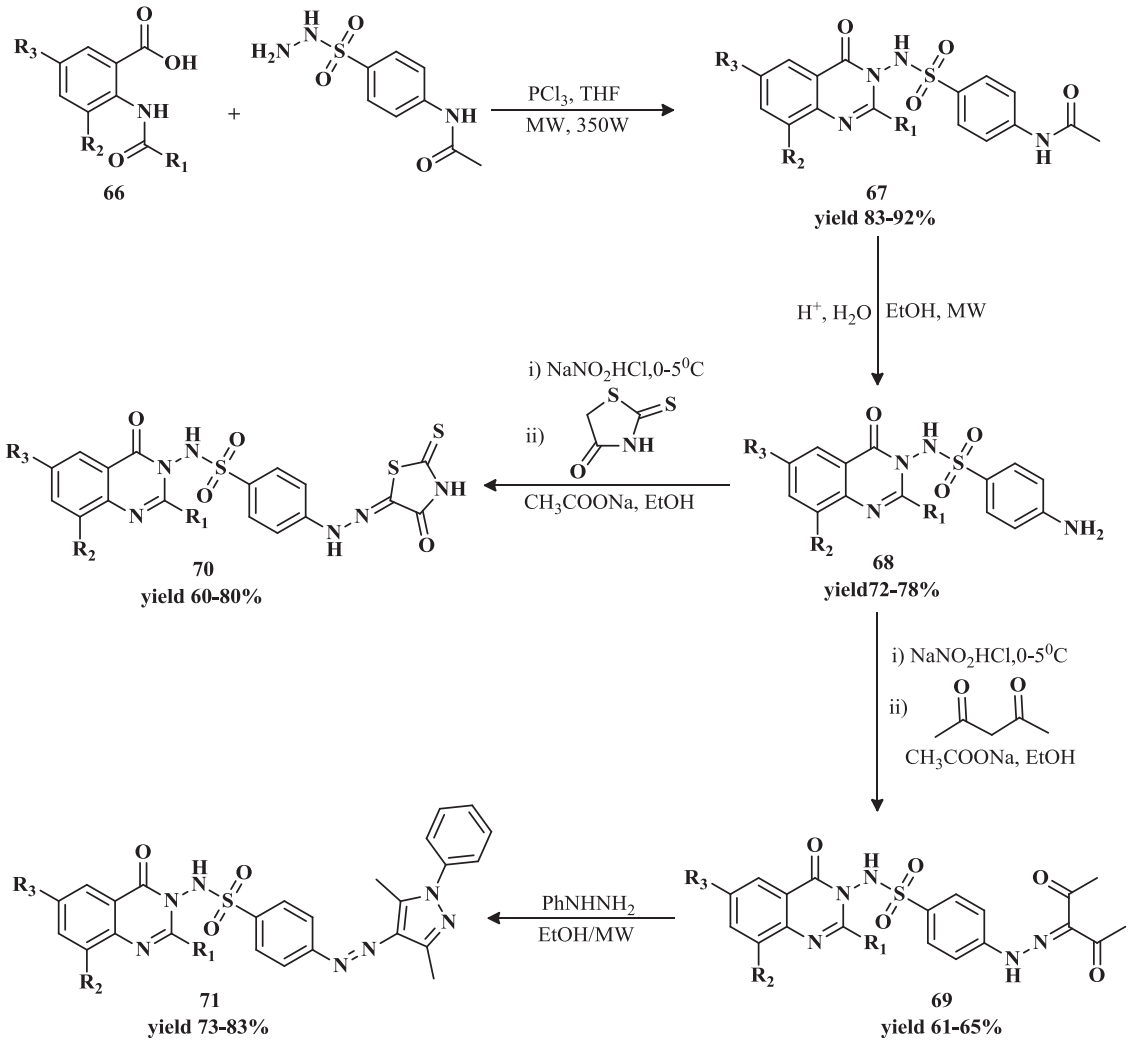
R_1 = C_6H_5, CH_2,$CH_2C_6H_5$, Bn, 2-Thiophenemethylene, C_6H_4-4-CO_2H, C_6H_4-4-OCF_3, C_6H_3-3,4-Cl, C_6H_4-4-CF_3, C_6H_4-4-CN, C_6H_4-4-Cl, C_6H_3-3-NO_2-4-Cl, $C_6H_{4\text{-}43}$-CO_2H, C_6H_4-4-*i*-Pr, C_5H_4-4-OCH_3, C_5H_3-3,4-F, C_6H_4-4-Cl, C_6H_3-3,4-OCH_3, C_6H_3-3,4-Cl, C_6H_4-4-F, C_6H_4-4-NO_2, C_6H_2-2,3-Cl-5-CH_3, C_6H_3-2,4-Cl, Bn, t-Bu

Scheme 24 A synthetic approach for 3-substituted quinazolin-4-one derivatives (**61**)



Ar = C_6H_5, C_6H_4-4-CH_3, C_6H_4-4-OCH_3, C_6H_4-4-Cl, C_6H_4-4-NO_2, C_6H_4-3-NO_2, C_6H_4-2-NO_2, C_6H_2-2,3,4-OCH_3, R_1 = R_2 = H, Br

Scheme 25 A synthetic approach for (*E*)-4-amino-*N*-(4-oxo-2-substituted styrylquinazolin-3(4*H*)-yl)benzenesulfonamide (**65**)



R_1 = CH_3, C_6H_5, C_6H_4-4-Cl, R_2 = H, Br, R_3 = H,Br, NO_2

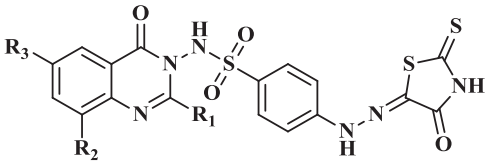
Scheme 26 Synthetic approaches for rhodanine substituted quinazolinones (**70**) and pyrazole substituted quinazolinones derivatives (**71**)

streptomycin, and nystatin drugs against all pathogenic bacteria (Fig. 7, Table 15).

Synthesis of *N*-sulfonylamino 1*H*-quinazoline-2,4-dione derivatives

In search for new scaffolds endorsing AMPA receptor antagonism, several patents and reports was published for the preparation and pharmaceutical uses of 1*H*-quinazoline-2, 4-diones in treating neuronal ceroid lipofuscinosis. The first patent that related to the preparation of *N*-sulfonylamino quinazoline-2,4-diones was filed by Allgeier et al. (2006a). As a shown in Scheme 28, treatment the substituted anthranilic esters 72 with phosgene afforded the isocyanates 73 which then reacted with different sulfonyl hydrazides in THF at room temperature for 4 h. Ring closure was achieved via adding aqueous sodium hydroxide solution to the reaction mixture, leading the desired 1H-quinazoline-2, 4-dione 74 in low to high yield (Scheme 27). An significant results was obtained by Koller et al. (2011), who represented some of synthesized *N*-sulfonylamino quinazoline-2,4-diones as a new class of competitive AMPA receptor antagonists.

Authors revealed that Introducing an imidazole group in position 6 through the direct replacement of the fluorine with imidazole in 7-nitro-2,4-quinazolinedione **75** enhanced the affinity as well as the selectivity to the AMPA receptor (Scheme 28).



70

a) $R_1 = C_6H_4$-4-Cl, $R_2 = H$, $R_3 = H$
b) $R_1 = C_6H_4$-4-Cl, $R_2 = H$, $R_3 = Br$
c) $R_1 = C_6H_4$-4-Cl, $R_2 = Br$, $R_3 = Br$

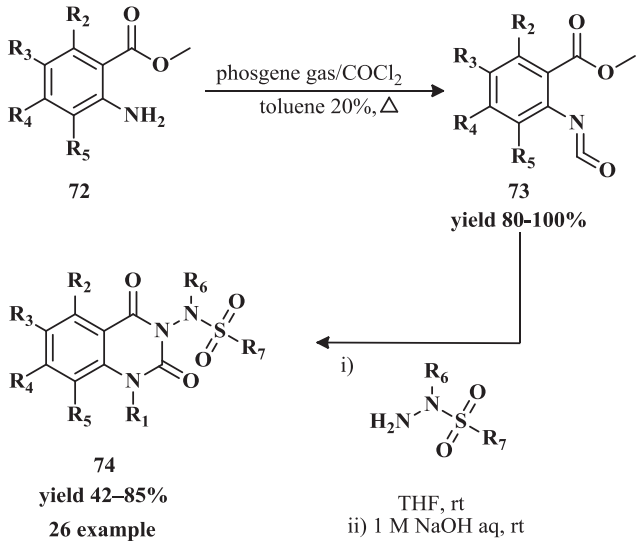
Fig. 7 The most active compounds **70a–c** against diverse microbial strains

Table 15 The MIC of the most potent compounds **70a–c**

MIC (μg/mL)									
Comp.	Gram (−ve) bacteria			Gram (−ve) bacteria			Fungi		
	EC	PV	PA	SA	BS	BM	AN	AC	CA
70a	50	75	100	120	120	150	75	100	175
70b	75	100	150	200	200	250	100	150	200
70c	50	100	125	150	175	250	150	150	175
Qm	400	400	450	350	375	375	475	475	500
Sf	375	400	425	375	400	475	475	450	500
Sm	20	20	20	20	20	20	–	–	–
Ny	–	–	–	–	–	–	60	60	60

All the tested bacteria: SA, *S. aureus*; BS, *B. subtilis*; BM, *B. megaterium*; EC, *E. coli*; PV, *P. vulgaris*; PA, *P. aeruginosa*; AN, *A. niger*; AC, *A. clavatus*

Standard drugs: Methaqualone (Qm) and Sulfanilamide (Sf), Streptomycin (Sm), and Nystatin (Ny)



72

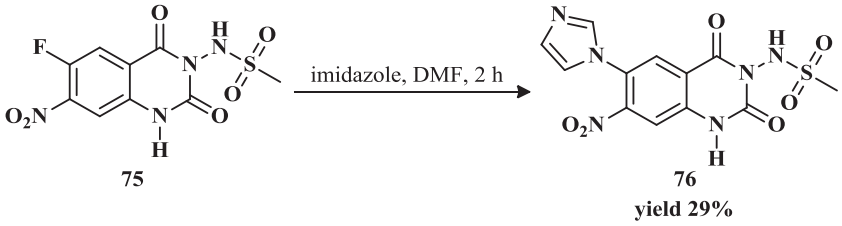
73
yield 80-100%

74
yield 42–85%
26 example

R_1 = H, Cl, R_2 = H, Cl, R_3 = H, Cl, R_4 = H, CH_3, Cl, CN, CF_3, NO_2, Br, OCH_3, F, CH_3SO_2, COOH, C_2H_5, CH_2=CH-, C_5H_5, *t*Bu, Bn, R_5 = H, Cl, R_6 = H, CH_3, R_7 = CH_3, C_2H_5, C_6H_5, N-Methyl-(4)-imidazolyl

Scheme 27 A synthetic approach for *N*-sulfonylamino quinazoline-2,4-diones (**74**)

Scheme 28 The direct replacement of the fluorine with imidazole in 7-nitro-2,4-quinazolinedione (**75**)



75 → **76**, yield 29%

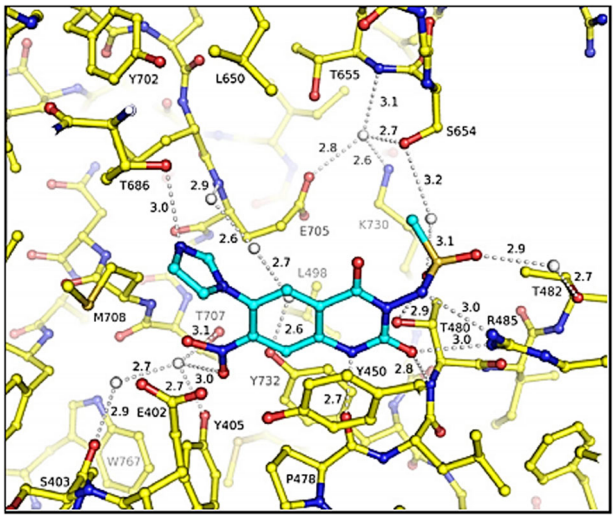
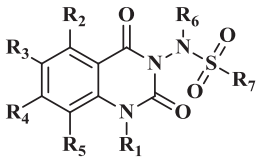


Fig. 8 X-ray structure at 2.1 Å resolution of the radioligand [^{3}H] CNQX binding domain of a hGluA2 construct (carbons in yellow, nitrogens in blue, oxygens in red and sulfurs in brown) bound to compound **76** (carbons in cyan). Selected interactions (distances in Å) and water molecules are shown in white



74a: $R_1 = R_2 = R_3 = H$, $R_4 = CH_3$, $R_5 = R_6 = H$, $R_7 = CH_3$
b: $R_1 = R_2 = R_3 = H$, $R_4 = C_2H_5$, $R_5 = R_6 = H$, $R_7 = CH_3$
c: $R_1 = R_2 = R_3 = H$, $R_4 = Cl$, $R_5 = R_6 = H$, $R_7 = CH_3$
d: $R_1 = R_2 = R_3 = H$, $R_4 = t\text{-}Bu$, $R_5 = R_6 = H$, $R_7 = CH_3$
e: $R_1 = R_2 = R_3 = H$, $R_4 = CF_3$, $R_5 = R_6 = H$, $R_7 = CH_4$
f: $R_1 = R_2 = R_3 = H$, $R_4 = OCH_3$, $R_5 = R_6 = H$, $R_7 = CH_3$
76: $R_1 = R_2 = H$, $R_3 = 1\text{-}Imidazoly$, $R_4 = NO_2$, $R_5 = R_6 = H$, $R_7 = CH_3$

Fig. 9 The synthesized compounds **74a–f**, **76** with interesting anticonvulsant effects against E-shock induced seizures after oral administration in mice

Table 16 Binding affinity of the synthesized compounds **74a–f**, **76**, and anticonvulsant effects of them against E-shock induced seizures after oral administration in mice (pretreatment time 60 min)

Comp.	AMPA [IC_{50}(μM)]	Anticonvulsant effects against E-shock induced seizures ED_{50} [mg/kg]
74a	**9.7**	**9**
74b	3.0	16
74c	2.4 ± 0.8	23
74d	4.9	29.5
74e	0.92 ± 0.08	54
74f	3.7	60%[a]
76	0.082 ± 0.001	40%[b]

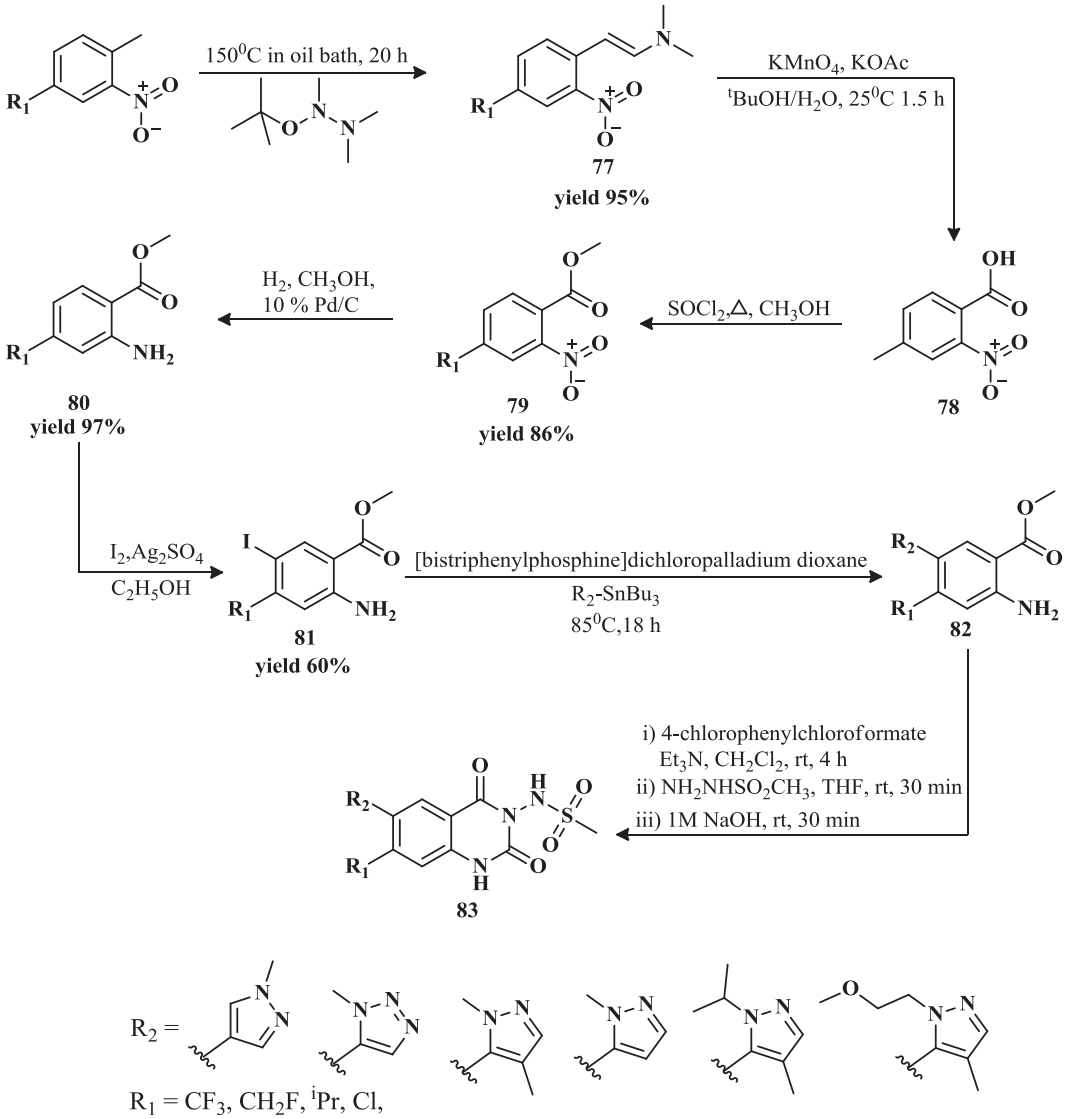
[a]Inhibition after oral administration of 30 mg/kg

[b]Inhibition after intraperitoneal administration of 30 mg/kg 28 is orally inactive against sound induced seizures in DBA/2 mice)

Compound **76** displayed highest receptor affinity due to the formation of hydrogen bond between the imidazole ring at position 6 and the side chain hydroxyl group of Thr686 and the main contribution of the adjacent nitro group in water mediated contacting to Tyr405 and Thr707 as a shown in X-ray structure of compound **76** co-crystallized with the human receptor hGluA (Fig. 8).

The most potent synthesized compounds, which displayed IC_{50}-values of 0.082–9.7 μM for the AMPA receptor within highly binding affinity at the AMPA receptor, investigated their oral anticonvulsant effects against E-shock induced seizures in mice (Fig. 9). All the selected compounds showed superior ability to inhibit E-shock induced seizures after oral administration except compound **76**. It is noteworthy that the oral ED_{50}-values of the tested compounds were found to be not directly correlated to the compounds affinities. For example, compound **76** showed nanomolar receptor affinity but was devoid of oral activity as well as required high intraperitoneal doses for inhibition of E-shock induced convulsions in mice. This disappointing result may attribute with the higher polar surface area (PSA) of compound **76** (164 Å) as comparing to the PSA of the orally potent compounds (101–110 Å2). Although, this increase in PSA suggested strengthen the receptor interactions, this hamper absorption/distribution, and particularly, the brain penetration of the compound (Table 16).

In continuation of designing 1*H*-quinazoline-2,4-dione sulfonamide analogs as potent and orally bioavailable AMPA antagonists, a synthetic approach for a set of novel *N*-sulfonyl amino quinazolinedione analogs from commercially available 4-substitiuted 1-methyl-2-nitrobenzenes was developed by Allgeier et al. (2006a, b). Initially, Vilsmaier reaction of available 4-substitiuted 1-methyl-2-nitrobenzenes afforded enamine intermediate **77**. The latter was oxidatively cleaved to carboxylic acid utilizing potassium permanganate and the resulting carboxylic acid **78** was then esterified to afford ester analog **79**. Reduction



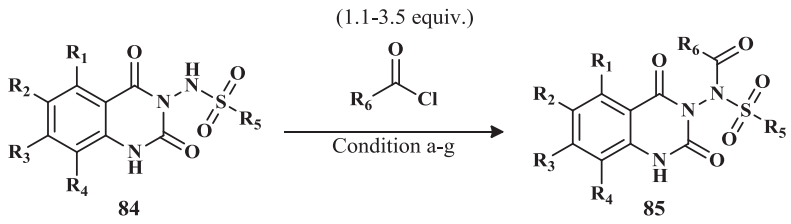
Scheme 29 A synthetic approach for novel 6-heteroaryl quinazoline-2,4-diones (**83**)

of the nitro group furnished the corresponding amino derivatives **80** which iodinated with iodine and silver sulfate to yield **81** in moderate yield. The subsequent palladium-mediated carbon–carbon couplings of **81** with different heteroaryl stannane reagents furnished the corresponding 4-substiuted-5-heteroaryl-disubstituted 2-aminobenzoates **82**. Finally, acylation of **82** with 4-chlorophenylchloroformate formed the activated carbamate derivative, which was easily reacted with methanesulfonyl hydrazide to afford the desired 6-heteroaryl quinazoline-2,4-diones **83** after base-catalyzed cyclization (Scheme 29).

Orain et al. (2016) demonstrated that some of the synthesized compounds in Scheme 30 was orally bioavailable, abled to penetrate the blood brain barrier and bound to the target receptor (AMPA)· Compounds **83a–c** possessed low IC_{50} values against AMPA in a range of 0.086–0.25 µg/mL (Fig. 10). These compounds suppressed MES-induced generalized tonic–clonic seizures in rodents with ED_{50} values 18, 7.4, 7 mg kg^{-1}, respectively after 1 h pre-treatment. Clear differences appeared between these compounds when pre-treatment time was extended. The activity of compounds **83a**, **b** dropped after 4 h pre-treatment and disappeared after 8 h pre-treatment while the effect of compound **83c** lasted for at least 8 h in mice. Compound **83c** showed a highly selective and competitive AMPA receptor antagonist as well as had a low human microsomal clearance and good mouse pharmacokinetic profile (Table 17).

Selectivity of compound **83c** for the AMPA receptor versus other ionotropic receptors was evaluated (Table 4). Compound **83c** allowed to inhibit the binding of radioligands to the glutamate ([^{3}H]CGP39653) as well as

Scheme 30 A synthetic approach for *N*-acylated analogs of *N*-sulfonylamino quinazolinones (**85**)



Condition a: i) $N(CH_2CH_3)_3$ (1.5 equiv.) CH_3CN, rt, 1.5 h
ii) $N(CH_2CH_3)_3$ (0.55 equiv.) CH_3CN, rt, 1.5 h
b: NaH ($1.1^{-2.2}$ equiv.) THF, rt, 1h
c: pyridine (1.9 equiv.) rt, 1 h

Condition d: pyridine (1.25 equiv.) DCM, rt, 1 h
e: $N(CH_2CH_3)_3$ (2.5 equiv.) DCM, rt, 1.5h
f: diisopropyl-ethylamine (1.2-2.2 equiv.) DCM, rt, 1.5 h
g: EDC (1 .25 equiv.), HOAt (1 .5 equiv.) $N(CH_2CH_3)_3$ (2.5 equiv.), DCM, rt, 2h

Fig. 10 The synthesized compounds **83a–c** with promising anticonvulsant effects against MES-induced generalized tonic–clonic seizures in rodents

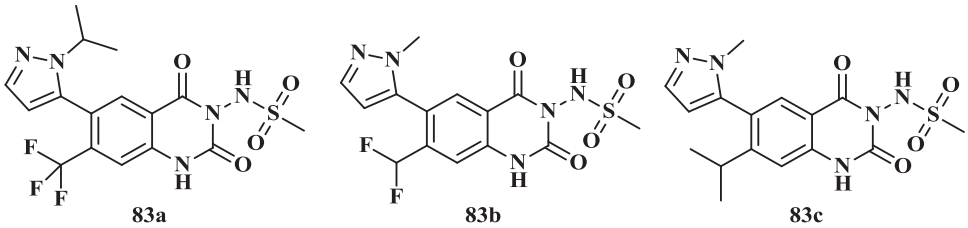


Table 17 Binding affinity and in vivo activity of the most potent quinazolinediones **83a–c** against MES-induced generalized tonic–clonic seizures in rodents

Comp.	IC_{50} (μg/mL)[a]	MES p.o. ED_{50} [mg kg^{-1}][b]		
		1 h	4 h	8 h
83a	0.086 ± 0.03	18	28	NE
83b	0.25 ± 0.05	7.4	20%[c]	NE
83c	0.19 ± 0.05	7	11	25.5

[a]Rat AMPA [^{3}H]CNQX binding

[b]Maximal electroshock seizure test in mice

[c]Percent inhibition at 50 mg kg^{-1} p.o., NE: not effective at 50 mg kg^{-1} p.o

Table 18 Binding of **83c** and reference compounds to iGluRs

Comp.	AMPA IC_{50} (μM)	NMDA glu IC_{50} (μM)	SR	NMDA gly IC_{50} (μM)	SR	Kainate IC_{50} (μM)	SR
DNQX	0.5	40	80	9.5	19	2.3	4
Kynurenic acid	101	184	1.8	20	0.2	>1000	>10
83c	0.186	>100	>540	27	145	>100	>540

glycine ([^{3}H]MDL105519) sites of the NMDA receptor but only at much higher concentrations (Table 18).

The X-ray crystal structure of compound **83c** bound to the AMPA receptor hGluA was identified. A favorable π–π stacking interaction with Tyr450 and a hydrogen bond network with residues Thr480, Arg485, and Pro478 were formed via the central scaffold of 1S. An additional hydrogen bond with Thr686 was also made. The isopropyl group formed van der Waals interactions with hydrophobic parts of Y405, E402, M708, and P478 (Fig. 11).

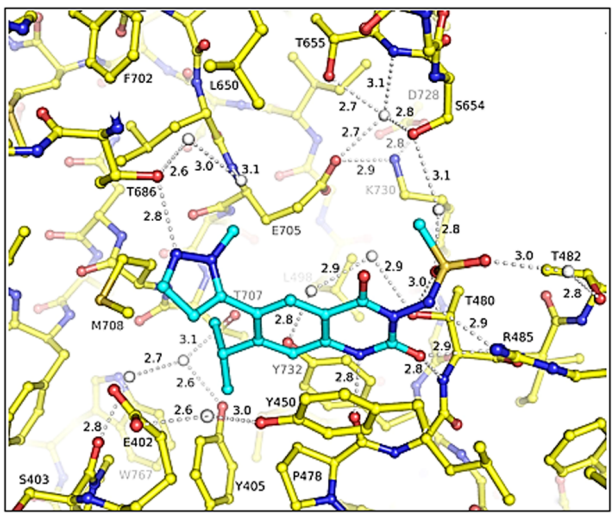
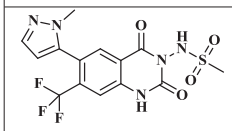
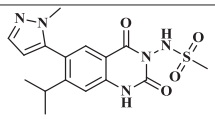
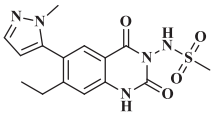
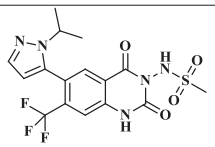
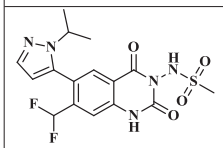
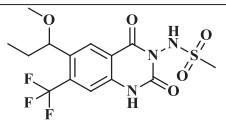
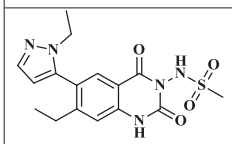
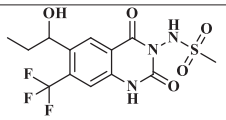
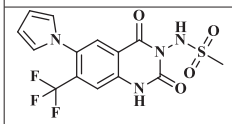
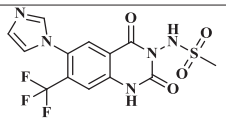
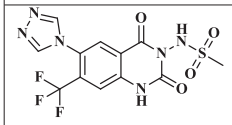
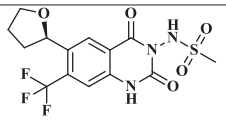


Fig. 11 X-ray crystal structure at 1.65 Å resolution of the ligand binding domain of an hGluA construct (carbon atoms in yellow, nitrogen atoms in blue, oxygen atoms in red, and sulfur atoms in brown) bound to compound **83c** (carbon atoms in cyan)

After research investigation of the all patents concerning the pharmaceutical uses of *N*-sulfonylamino 1*H*-quinazoline-2,4-diones in the treatment of any disorder or clinical condition including AMPA receptor mediated neuronal

Table 19 Receptor affinity and in vivo activity of different *N*-sulfonylamino quinazolinones in the murine maximal electro shock test

Comp.	[3H]CNQX IC_{50} [μM] AMPA receptor binding	%-Inhibition 50mg/kg, p.o. Pre-treatment time 1h	Comp.	3H]CNQX IC_{50} [μM] AMPA receptor binding	%-Inhibition 50mg/kg, p.o. Pre-treatment time 1h
	0.208	20		0.189	100, 6.9[a]
	0.257	80, 6.1[a]		0.087	80,17.7[a]
	0.110	80[b], 20[c]		0.317	100, 20.3[a]
	0.341	100,20.3[a]		0.162	40
	0.162	40		0.042	0
	.046	20[b]		0.159	100, 12.8

[a]Pre-treatment time: 2 h

[b]Dose: 25 mg/kg, p.o.

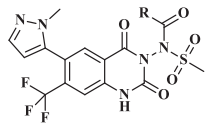
[c]Dose: 15 mg/kg, p.o.

damage or altered AMPA receptor function, we summarize the synthesized 1*H*-quinazoline-2,4-dione sulfonamides which investigated their in vivo efficacy to inhibit MES-induced generalized tonic–clonic seizures in OF1mice at dose of 50 mg/kg as well as their AMPA receptor binding affinities in Table 19 (Kalkman and Mattes 2012; Allgeier et al. 2011, 2014). The tested compounds showing potency exceeding to 60% inhibition after 1 h pre-treatment time at dose of 50 mg/kg calculated their effective doses (ED_{50}).

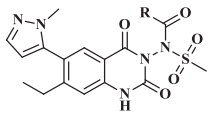
In an interesting patent, Auberson et al. (2011) claimed in their invention the *N*-acylated analogs of all compounds which listed above in Table 21 and studied their efficacy on inhibition MES-induced generalized tonic–clonic seizures in mice after 1 h pretreatment time at 50 mg/kg representing in Table 20. The acylation of nitrogen atom of sulfonamide moiety in 1*H*-quinazoline-2,4-dione sulfonamides **84** with a wide range of acid chloride derivatives was performed in the presence of a proper base at room temperature. Different bases and solvents were employed for proceeding acetylation process depending on the type of acid chloride (Scheme 30).

In continuation, Allgeier et al. (2006b) prepared and claimed more functionalized analogs in another patent. In this patent, 6-fluoro7-nitro 1*H*-quinazoline-2,4-dione **75** was used as a precursor for the synthesis of functionalized quinazoline-2,4-dione derivatives **87, 89**. 6-Fluoro7-nitro-2,4-quinazolinedione **75**, could efficiently underwent substitution reaction with different alkyl, cycloalkyl, aryloxy, and aralkyloxy amines **86** under heating in microwave reactor at 150 °C for 5 min and 20 h to produce functionalized 1*H*-quinazoline-2,4-diones **87** in moderate yield. On the other hand, An alternative condition was utilized to react quinazoline-2,4-dione **75** with a wide range of imidazole

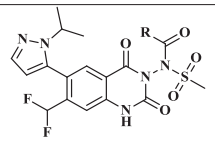
Table 20 In vivo activity of diverse *N*-acylated quinazolinone sulfonamides at 50 mg/kg in the murine maximal electro shock test (MES test) after oral administration in mice



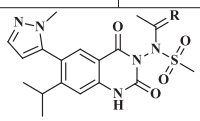
R	%Inhibition
$(CH_2)_3CH_3$	40
$CH(CH_3)CH_3$	100
$(CH_2)_2CH_3$	100
$(CH_2)_4CH_3$	80
OCH_3	80
$OCH_2CH(CH_3)CH_3$	60
$O(CH_2)_2OCH_3$	80



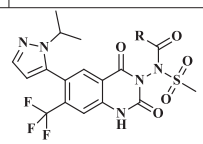
R	%Inhibition	R	%Inhibition	R	%Inhibition
CH_3	100	$(CH_2)_2CH_3$	100[b]	OC_2H_5	80
$(CH_2)_2CH_3$	100[b]	$(CH_2)_3CH_3$	100[b]	$O(CH_2)_3CH_3$	40
CH_2CH_3	100	$CH_2CH(CH_3)_2$	80[b]	$(CH_2)_3CH_3$	100
$OCH(CH_3)_2$	60	$(CH_2)_2OCH_3$	80[b]	$OCH(CH_3)_2$	60
$O(CH_2)_4CH_3$	20	OCH_3	100		



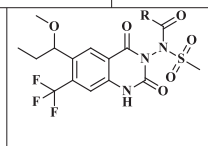
R	%Inhibition	R	%Inhibition
CH_3	80,20[b]	$O(CH_2)2OCH_3$	40
$(CH_2)_2CH_3$	40,20[b]		
$(CH_2)_3CH_3$	40,0[b]		
$O(CH_2)2CH_3$	20,0[b]		
CH_2CH_3	80,60[b]		
OCH_2CH_3	60,20[b]		



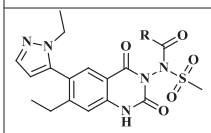
R	%Inhibition	R	%Inhibition
CH_3	100	$(CH_2)_8CH_3$	20[e]
$O(CH_2)_2OCH_3$	100[c]	$CH(CH_3)CH_3$	60
$OCH_2CH(CH_3)CH_3$	40[c]	CH_2OCOCH_3	100
OCH_3	60[c]	$(CH_2)_2SCH_3$	100
$(CH_2)_2CO_2CH_2CH_3$	100[c]	OCH_2CH_3	100
$CH_2CO_2CH_2CH_3$	80[c]	$O(CH_2)_2CH_3$	100
$(CH_2)_3CO_2CH_2CH_3$	100[c]	$O(CH_2)_3CH_3$	100
$(CH_2)_3CH_3$	100[c]	$O(CH_2)_5CH_3$	100
CH_2CH_3	100	$C(CH_3)_3$	20
$(CH_2)_2CH_3$	100	$CH_2OCH_2C_6H_5$	100
$(CH_2)_4CH_3$	100	$(CH_2)_3OCH_2C_6H_5$	100



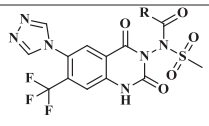
R	%Inhibition
CH_3	60
CH_2CH_3	20
$(CH_2)_2CH_3$	40
$(CH_2)_4CH_3$	20
$CH(CH_3)CH_3$	60
OCH_2CH_3	60
$O(CH_2)_2OCH_3$	40
$O(CH_2)_3CH_3$	40
$CH_2CO_2CH_2CH_3$	40
$(CH2)_2SCH_3$	40



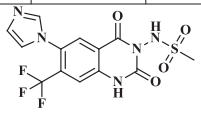
R	%Inhibition
$O(CH_2)OCH_3$	60
CH_2CH_3	100
OCH_2CH_3	80
$OCH(CH3)_2$	60
$O(CH_2)_4CH_3$	80
$CH(CH_3)_2$	100
$(CH_2)_2CH_3$	100
CH_3	80
OCH_3	80
$CH_2CH(CH_3)_2$	100
$O(CH_2)_3CH_3$	60
$O(CH_2)_5CH_3$	60
$(CH_2)_3CH_3$	100



R	%Inhibition
$CH_2CH(CH_3)_2$	20
$(CH_2)_4CH_3$	20
CH_2CH_3	20

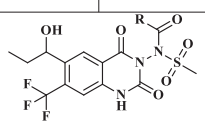


R	%Inhibition
$CH_2CH(CH3)_2$	40[a]
$(CH_2)_4CH_3$	20[a]
$(CH_2)_3CH_3$	20
$(CH_2)_2CH_3$	20[a]

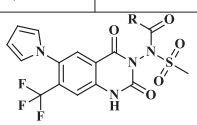


R	%Inhibition
$(CH_2)_2CO_2CH_2CH_3$	20
$(CH_2)_3CH_3$	100
CH_3	40
CH_2CH_3	40[a]

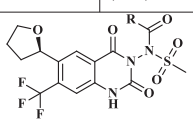
R	%Inhibition
$CH(CH_3)_2$	80
$CH_2CH(CH_3)_2$	20
$(CH_2)_4CH_3$	20
$(CH_3)_2CH_3$	40



R	%Inhibition
$(CH_2)_4CH_3$	40
$(CH_2)_2CH_3$	40
$CH(CH_3)_2$	40
$(CH_2)_3CH_3$	40



R	%Inhibition
$(CH_2)_2CH_3$	20
CH_2OCOCH_3	40
OCH_3	20
OCH_2CH_3	80



R	%Inhibition
CH_3	80,40[d]
CH_2CH_3	60,60[d]
$(CH_2)_2CH_3$	100,60[d]
OCH_3	20

R	%Inhibition
OCH_2CH_3	40
$O(CH_2)_3CH_3$	40
$(CH2)2OCH_3$	60
$(CH_2)_4CH_3$	60

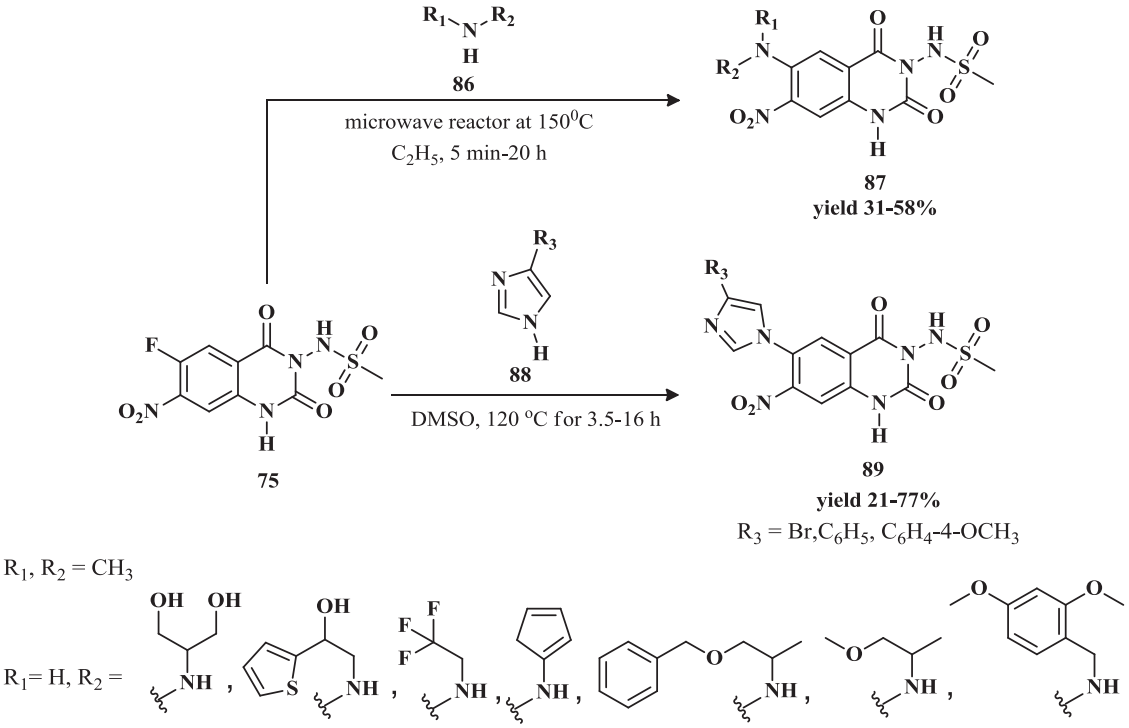
[a]Pre-treatment time: 2 h

[b]Dose: 25 mg/kg, p.o.

[c]Dose: 15 mg/kg, p.o.

[d]Pre-treatment time: −0.5 h

[e]Dose: 25 mg/kg, s.c, pre-treatment time: 4 h



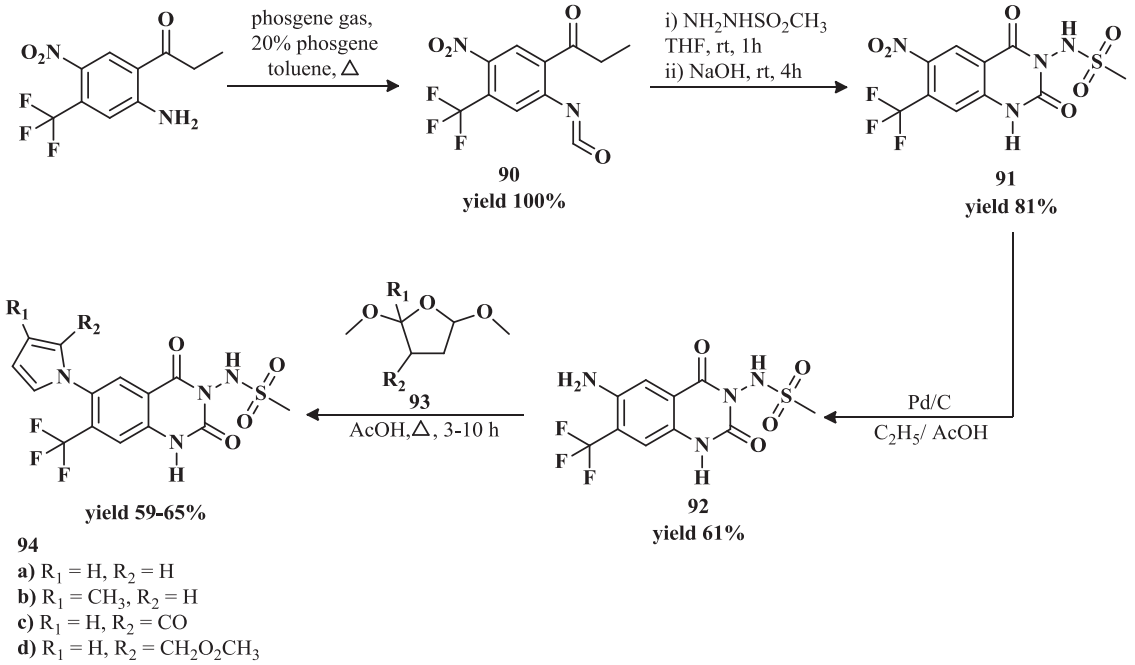
Scheme 31 Synthetic approaches for 6-substituted 1*H*-quinazoline-2,4-diones(**87**, **89**)

derivatives **88** based on heating the reactants in DMSO at 120 °C for 3.5–16 h to obtain heterocycloaryl 1*H*-quinazoline-2,4-diones **89** in low to good yield (Scheme 31).

For more access functionalized 1*H*-quinazoline-2,4-dione analogs, 6-amino-7-trifluoromethyl-1*H*-quinazoline-2,4-dione **92** was subjected to reflux with a verities of tetrahydrofuran derivatives **93** for 3–10 h. To prepare 1*H*-quinazoline-2,4-dione **92**, 6-nitro-2*H*-quinazoline-2,4-dione analog **91** was firstly prepared from 5-fluoro-2-nitro-4-trifluoromethyl-benzoic acid methyl ester in analogy to synthetic pathway mentioned previously in Scheme 30 and then hydrogenated the resulting 6-nitro-1*H*-quinazoline-2,4-dione **91** (Scheme 32) (Allgeier et al. 2006a, b).

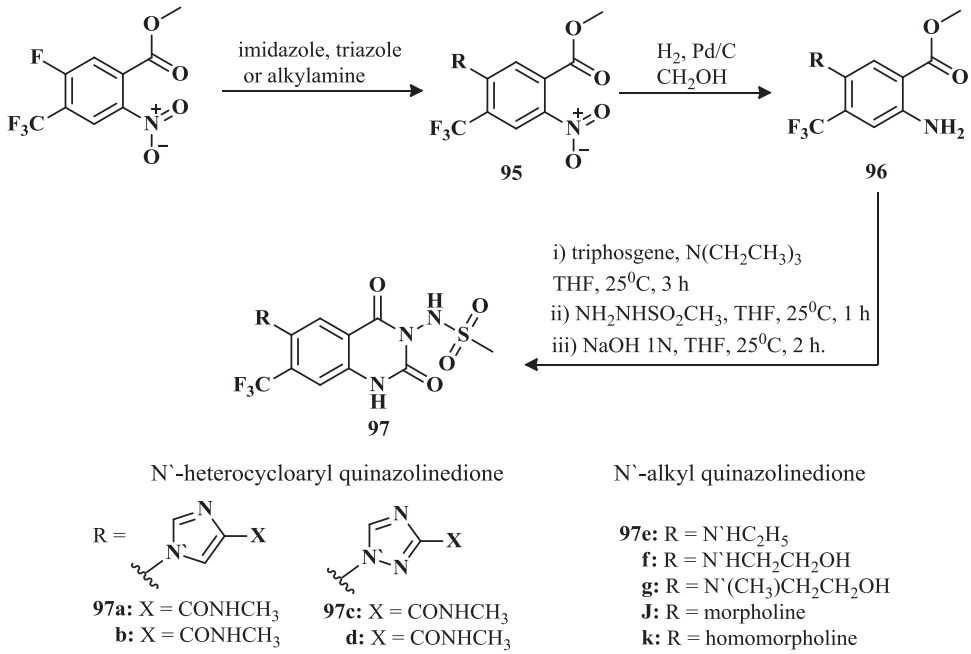
In continuous research in this field, Orain et al. (2012) studied the effect of diverse *N*′-alkyl/heterocycloaryl 1*H*-quinazoline-2,4-dione sulfonamides **97a–k** in receptor binding affinity using rat brain homogenates and the radioligand [^{3}H]-CNQX as well as inhibition of audiogenic seizures in DBA/2 mice. The synthesis of *N*′-alkyl/heterocycloaryl quinazolinediones **97a–k** was required several steps. Firstly, methyl 5-fluoro-2-nitro-4-(trifluoromethyl)benzoate underwent nucleophilic aromatic substitution with a wide variety of 4-substituted imidazoles, 4-substitued-1,3,5-triazoles and alkylamine, providing 5-alkyl/heterocycloaryl-2-nitro-4-(trifluoromethyl)benzoate **95**. The reduction of **95** afforded the nitro derivatives **96**. Finally, acylation of the nitro derivatives **95** with triphosgene following by base catalyzed-cyclocondensation with methanesulfonyl hydrazide furnished the desired quinazolinediones **97** (Scheme 33).

The results showed that monomethylamide analog **97a** was found to be the best synthesized compound in terms of receptor affinity in nanomolar concentration ($IC_{50} = 14$ nM) but demonstrated poor in vivo efficacy after oral dosage. Despite, *N*-alkylated compounds **97e–k** showed submicromolars to micro-molars affinities, these compound exhibited significant anticonvulsant activity in the audiogenic seizures 1 h after oral administration especially



Scheme 32 A synthetic approach for more analogues of 6-substiuited 1*H*-quinazoline-2,4-diones (**94**)

Scheme 33 A synthetic approach for *N′*-alkyl/ heterocycloaryl 1*H*-quinazoline-2,4-dione sulfonamides (**97**)



compound **97k**. Compound **97k** inhibited convulsions of the hind legs with 5.5 mg/kg ED_{50}-value (Table 21).

By the aid of X-ray analysis for **97a** co-crystallized with a construct of hGluA human receptor, Authors explained the high receptor affinity of compound **97a**. It was attributed to an additional hydrogen bond was identified between N–H amide and Glu402 (Fig. 12).

Significant results obtained from preclinical data indicating superior effectives of some quinazolinedione

Table 21 Receptor affinity and *in-vivo* efficacy in DBA/2 mice of the most potent compounds **97a, e–k**

Comp.	[^{3}H]CNQX (nM)	Audiogenic seizure ED_{50} (mg/kg)
97a	14 ± 2	10% at 30
97e	1000 ± 200	53% at 30
97f	550 ± 10	20% at 10
97g	250 ± 100	7.9
97j	500 ± 80	58
97k	360 ± 90	5.5

Table 22 Improvement in pain as evaluated by the Patient Migraine Diary (PD cohort)

The used prodrug and drugs	Time (h)	Headache improvement to mild or no pain			≥2-point improvement		Pain-free	
		Response rate	90% CI, LL; UL	*p* value[a]	Response rate	*p* value[a]	Response rate	*p* value[a]
Selurampanel	2	14 (58.3%)	0.41; 0.73	0.2020	7 (29.2%)	0.2753	6 (25.0%)	0.4377
	3	14 (58.3%)	0.41; 0.73	0.4695	9 (37.5%)	0.1807	9 (37.5%)	0.0961
	4	13 (54.2%)	0.38; 0.70	0.4774	13 (54.2%)	0.0163	12 (50.0%)	0.0149
Sumatriptan	2	17 (68.0%)	0.51; 0.81	0.0502	10 (40.0%)	0.0660	6 (24.0%)	0.4820
	3	21 (84.0%)	0.68; 0.93	0.0102	13 (52.0%)	0.0221	9 (36.0%)	0.1147
	4	23 (92.0%)	0.77; 0.97	0.0014	16 (64.0%)	0.0026	12 (48.0%)	0.0197
Placebo	2	10 (40.0%)	0.25; 0.57	–	4 (16.0%)	–	4 (16.0%)	–
	3	12 (48.0%)	0.32; 0.64	–	5 (20.0%)	–	4 (16.0%)	–
	4	11 (44.0%)	0.29; 0.60	–	5 (20.0%)	–	4 (16.0%)	–

PD pharmacodynamic, *N* number analyzed, *CI* confidence interval, *LL* lower limit, *UL* upper limit

[a]Compared with placebo

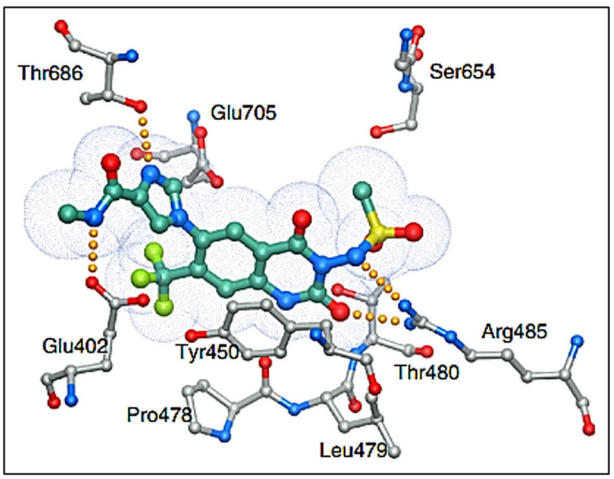


Fig. 12 X-ray structure at 1.9 Å resolution of the ligand binding domain of a GluA2 construct (extracellular domain) bound to **97a**—selected interactions are shown in orange

sulfonamides, including the synthesized compound **83c** in both of the DBA/2 audiogenic seizure mouse model and mouse maximal electroshock seizure (MES) model. Particular focus was accomplished by Zielinski et al. (2012) on fomulation comprising *N*-sulfonylamino 1*H*-quinazoline-2,4-dione **83c** in the form of immediate release tablet. The titled compound **83c** in this review is also known as selurampanel. Randomized, multicenter trial was done to assess the efficacy and tolerability of a single dose of a new AMPA receptor antagonist selurampanel (250 mg) in 75 subjects with acute migraine attacks (Gomez-Mancilla et al. 2014). This study proved that an enhancement from severe/moderate to mild/no headache pain was observed in 58%, 58%, and 54% of selurampanel-treated subjects at 2, 3, and 4 h post-dose, respectively as compared with 68, 84, and 92% sumatriptan-treated subjects, as well as 40, 48, and 44% in the placebo group (Table 22). Selurampanel was found to be comparable to sumatriptan in terms of sustained responses and pain-free. However, the most common treatment-emergent adverse effects of selurampanel in this clinical trial were somnolence and dizziness. No more clinical studies have yet appeared and selurampanel is still under clinical investigation.

Data presented as number of subjects and percentage of total in treatment group. Numbers include those that did not receive rescue medication before the given timepoint. ≥2-point improvement defined as an improvement from baseline of two or more on the four-point severity scale.

Conclusion

In light of the great therapeutic importance of sulfa drugs, reports advances made to access more analogs for these compound classes via linking sulfonamide moiety with nitrogen of azinones. As reported, several synthetic approaches were developed for the preparation of *N*-sulfonylamino azinones. Interestingly, most of the new generation *N*-sulfonylamino azinones demonstrated interesting biological potencies. Additionally, these compounds exhibited excellent profile in preclinical studies which reveals that these could be developed as competitive AMPA receptor antagonists. Numerous patents published during the last decade concerning with the biological activities of this type of sulfonamide analogs. In this review, we focus the synthesis of *N*-sulfonylamino azinones and their biological and preclinical significance in medicinal chemistry.

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