Study the pharmacological potential of 1,2,4-thiadiazine 1,1-dioxides: A minireview

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Abstract:

Study of the pharmacological activity of new heterocyclic scaffolds becomes a passion of many medicinal chemists around the world. 1,2,4-thiadiazine 1,1-dioxide derivatives are one of the heterocyclic derivatives that have attracted researchers' attention since the early 1940's. In spite of this, however, the study of the pharmacological activities of this nucleus remains scant and needs to shed lighter on it. Therefore, in this review, the authors in this review collected all the families that included this nucleus whose biological activities were studied for the period between 1993 and 2020 in order to get an idea of the effectiveness of these compounds and highlighted the most effective ones. In addition, knowing the pharmacological aspects that had not been studied previously to focus more on them in the future by interested researchers.

Key words: 1,2,4-thiadiazine, minireview, biological activity, Channel openers.

دراسة الاحتمالات الصيدلانيه لمركبات 1,2,4-ثياديازين 1,1-ثنائي الاوكسايد: مراجعه مصغرة

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***** قسم الكيمياء/ كلية العلوم/ الجامعه المستنصرية***

الخلاصة:

لقد أصبحت دراسة النشاط الدوائي للمركبات الحلقية غير المتجانسة شغفًا للعديد من الكيميائيين حول العالم. تعد مشتقات 1،2،4-ثياديازين 1،1 ثنائي أكسيد هي واحدة من المشتقات الحلقية غير المتجانسة التي جذبت انتباه الباحثين منذ أوائل الأربعينيات. وعلى الرغم من ذلك ، تظل دراسة الأنشطة الدوائية لهذه النواة شحيحة وتحتاج إلى إلقاء المزيد من الضوء عليها. لذلك ، في مقال المراجعة هذا، جمع المؤلفون في هذه المراجعة جميع العائلات التي تضمنت هذه النواة و التي تمت دراسة أنشطتها البيولوجية للفترة ما بين 1993 و 2020 من أجل الحصول على فكرة عن فعالية هذه المركبات وإبراز أكثرها فعالية. بالإضافة إلى معرفة الجوانب الدوائية التي لم يتم دراستها من قبل للتركيز عليها أكثر في المستقبل من قبل الباحثين و المهتمين.

الكلمات المفتاحية: 1,2,4-ثياديازين،مراجعه مصغرة،فعاليه حيويه،فاتحات القنوات

Introduction

During the last years, researchers of medicinal chemistry have focused on the development of heterocyclic compounds and study them as potential drug nominates [1-5]. Thiadiazines are type of heterocyclic derivatives that attracted the attention of many chemists and pharmacists. They have three constitutional isomers depend on the position of nitrogen and sulphur atoms, which are 1,2,4-thiadiazine, 1,3,4-

thiadiazine, 1,3,5-thiadiazine derivatives, Figure 1.

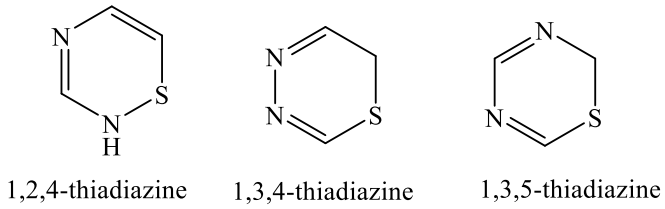


Figure (1): Constitutional isomers of thiadiazines.

These derivatives when fused to another cyclic compound's derivatives create new nucleus such as triazolothiadiazines, imidazothiadiazines, thienothiadiazines, benznothiadiazines, pyrazinothiadiazines, and pyridothiadiazines. Figure 2 shows some fused 1,2,4-thiadiazine nucleus.

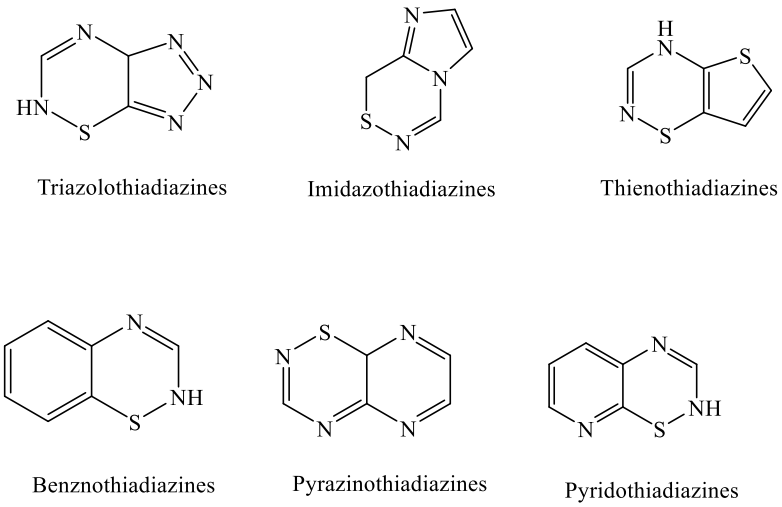


Figure (2): Some fused 1,2,4-thiadiazine nucleus.

Biological molecules and natural products are rich with 1,2,4-thiadiazine 1,1-dioxides moiety and they were studied since the forties of previous century. These compounds are poorly described in the literature and not so many articles studied their properties. That may be attributed to the chemical properties of these compounds or their method of preparations [6].

These fused nuclei revealed many medicinal properties and become very important for chemists and pharmacists since they showed anti-cancer, anti-bacterial, and anti-viral activities. Furthermore, they are known for their inhibitory activity for some enzymes such as non-nucleoside reverse transcriptase (NNRTIs) of type 1 Human Immunodeficiency Virus (HIV), Hepatitis C Virus Nonstructural protein 5B polymerase (HCV NS5B polymerase), aldose reductase, and xanthine oxidase. They also act as ATP-sensitive potassium channel openers and inhibited insulin release [7, 8, 10-13]. They are well known for their cardiovascular and diuretic as well as anti-hypertensive effects. They are used in treatment of cerebro and cognitive disorders [7]. In addition, some of these scaffolds are used to treat Alzheimer's at early stages [9]. Diabetes and obesity are also treated using these derivatives in some studies [8]. They exhibit potent

psychotropic and mycobacterium tuberculosis properties [7]. Additionally, they work as antifungal, as well as anticancer properties by inhibition of ribonucleotide reductase enzyme [14, 15].
For all of the above properties and since there is no previous published review article about the potential medicinal effects of 1,2,4-thiadiazine 1,1-dioxides, we try herein to summarize all biological activities of these scaffolds and highlight the best active compounds out of each synthesized family in the period between years 1993 and 2020.

Biological Activity

In the following sections different biological activities of 1,2,4-thiadiazine 1,1-dioxides families will be discussed and the chemical structure of more potent compound will be focused on as an example.

Potassium Channel Openers

Diazoxide (7-chloro-3-methyl-4*H*-benzo [*e*] [1,2,4] thiadiazine 1,1-dioxide) is a benzothiadiazine antihypertensive drug which is well known for its activity as ATP-sensitive potassium channel (K_{ATP}) openers. Potassium channels has main role for controlling the cell membrane physiological activities. Therefore, many researches during the last decades have been performed to discover new derivatives that working as good potassium channel openers and related to diazoxide (a druge used for management of hypoglycemia) chemical structure. As a result, a lot of scientists synthesized and studied the activity of novel 3-alkylamino-pyrido[4,3-*e*]-l,2,4-thiadiazine 1, l-dioxides which are structurally related to both diazoxide and pinacidil (two potent K_{ATP} channel openers) as shown in Figure 3. These derivatives will discussed in the following sections [6, 16 17].

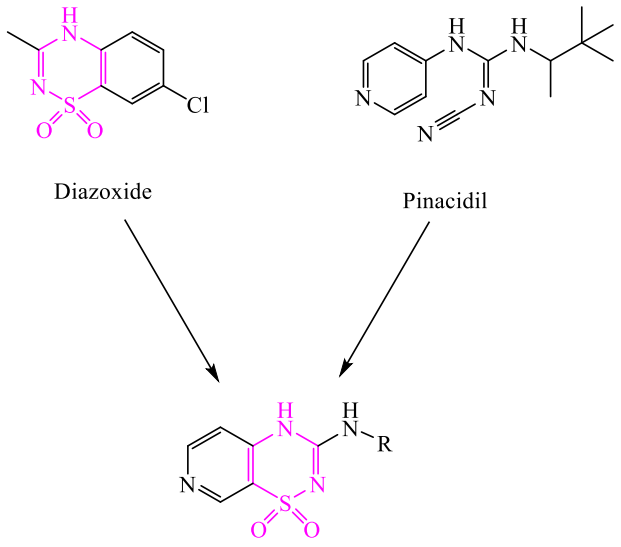
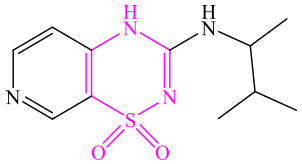


Figure (3): Three classes of potent K+ channel openers 17.

Different**3-(alkylamino)-4*H*-pyido[4,3-*e*]-1,2,4-**thiadiazine1,l-dioxides were synthesized by Pirotte B. in 1993 as good insulin inhibitors to prevent secretion of insulin from rat pancreatic β-cells. These derivatives were tested as inhibitors for insulin release from pancreas of rats when incubated with 16.7 mM glucose concentration comparing with diazoxide druge. Results showed that compounds (1) and (2) were the most powerful inhibitors of insulin release. These compounds were discovered to act as vasorelaxant on

potassium depolarized rat aorta at the same previous concentration [18].



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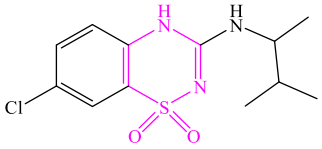
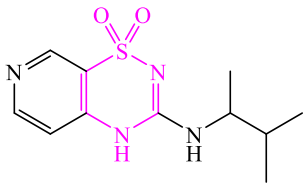


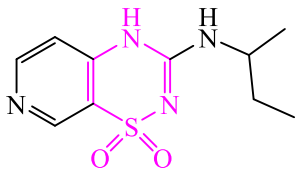
(2)

In another work, Piroite B. and colleagues in 1994 indicated that the [3-(1',2' dimethyl propyl) amino-4H-pyrido [4,3-e] [1,2,4] thiadiazine l,l-dioxide] (3), a new pyrido thiadiazine derivative, inhibit the process of insulin releasing in obvious way. These results revealed that the activation of ATP-sensitive K+ channels led to decrease in calcium (II) flowing, inhibition of insulin releasing, as well as reduction in cytosolic free calcium (II) concentration. These results considered as an attempt to consider pyrido thiadiazine scaffolds as good openers for KATP channels 19.



(3)

In addition, the same team led by Tullio P. in 1996 have synthesized pyridothiadiazines bearing a variety of 3-aminoalkyl side chains. The activities of these derivatives on isolated rat aorta as insulin inhibitor on β-cells of pancreas and vasorelaxants were studied comparing to diazoxide drug. Three different derivatives of 3-(alkylamino)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides which were compounds (3) **(**same as previous study**)** as well as (4), and (5) presented excellent insulin inhibitory and were more selected for the tissue of pancreas against tissues of vessels comparing with diazoxide drug or chlorobenzoic derivatives. The results of interactions of the most active derivatives (3, 4, and 5) with pancreatic K_{ATP} channels that proposed by pharmacophoric models can help to design new drugs working on specific tissues. Since derivatives can inhibit insulin secretion with lower effect on blood pressure in more powerful way than diazoxide, therefore they can be nominated as a good substituent for diazoxide in order to cure the disorders of pancreas release [20].



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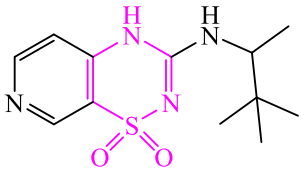
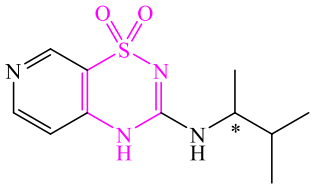


(5)

In another attempt, Khelili S. 1999 was described the synthesized 3-(3'-methyl-2'-butylamino)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (3) and 3-(2'-butylamino)-4*H*-pyrido[4,3-*e*]- 1,2,4-thiadiazine 1,1-dioxide (4) as a selective opener of adenosine triphosphate-sensitive potassium channel. The R- and S-isomers of (3) show approximately a comparable effect on β-cells of pancreas while their effect on the vascular smooth muscle (VSM) cells is greatly differ. On another

hand the effect of R-isomer of (4) on the endocrine pancreas is stronger than S-isomer. Also, the selectivity for tissue is also differ that the both isomer of (4) and S-(3) show selectivity toward pancreas tissue versus VSM cells [21]. In addition, one more study on the same compounds, both isomers of (3) and (4) exerted a potent inhibition effect on the secretion of insulin. That, these drugs completely inhibited insulin secretion at a concentration of 50 μM [17].



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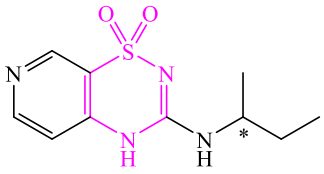
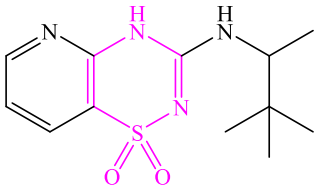


(4)

Another diazoxide and pinacidil structural analogues series of 3-alkylamino-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxides were synthesized by Pirotte B. and co-workers in 2000 and examined as opener for K_{ATP} receptor on different tissue such as *in vitro* pancreatic tissue, *in vitro* intestinal, uterine and VSM. Two compounds of this series (6) and (7), having pinacidil at side chain show the greater activity on rat aorta rings. Additional biological studies showed that both new derivatives (6) and (7) expressed classical K_{ATP} receptor opening activity since they have effect on 30 or 80 mM KCl-induced contractile activity, as well as the effects of glibenclamide on these two derivatives-induced responses. Those new discovers may recommend compounds (6) and (7) as new openers of K_{ATP} channel that have a comparable profile to pinacidil and diazoxide [22].



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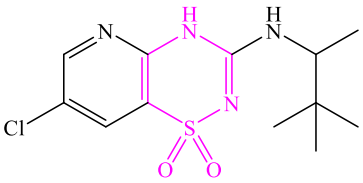
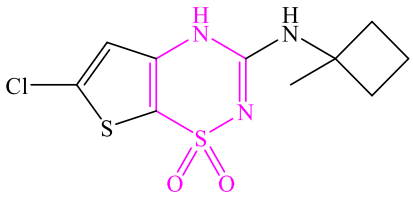


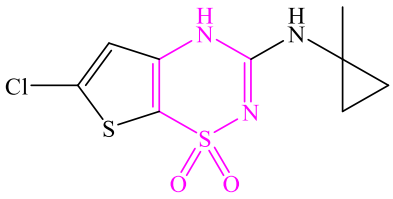
(7)

Additional study on series of 6-chloro-3-alkylamino-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide derivatives were performed by Nielsen F. E. 2002 who are responsible for synthesizing and characterizing new scaffolds as sensitizers of K_{ATP} channels in the β-cells through the measurement of *in vitro* reaction of membrane potential as well as secretion of insulin. One of the powerful scaffolds 6-Chloro-3-(1-methylcyclobutyl) amino-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine1,1 dioxide (8) can in a very small nanomolar concentration activate the SUR1/Kir6.2 K_{ATP} channels and be thousand times higher effective than the standard drug diazoxide in insulin inhibition secretion from rat islets. This compound may considered as potent activator of ATP-regulated potassium channels [23].



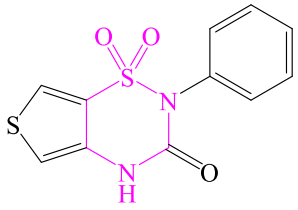
(8)

Nielsen F. E. and his team in 2006 improved new synthesis pathway to produce a series of 3-alkylamino-4*H*-thieno-1,2,4- thiadiazine 1,1-dioxides as promising stimulators of K_{ATP} by elaborating on the SAR. Compound (9) was the most powerful opener for channels of Kir6.2/SUR1 K_{ATP}. It was inhibited *in vitro* and *in vivo* insulin secretion and conserve β-cell function in special type of animal models. That can suggest compound (9) to be used in the management and prevention both types of diabetes (types I and II) [24].



(9)

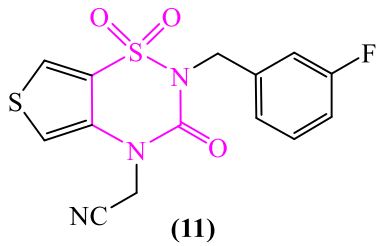
In one more study, producing of new potent derivatives of 2,3-dihydro-3-oxo-4*H*-thieno[3,4-*e*] [1,2,4] thiadiazine 1,1-dioxides by Arranz E. and his team and estimation of their biological activities as cardioactive potentials on cardiovascular system of rats were reported in 2000. The studied derivatives were synthesized from sulfamoylacylazides by Curtius reaction. These compounds were measured for their ability as voltage-dependent Ca-channel blockers. These thienothiadiazines worked in a similar way of diazoxide and they inhibited the continuous motion produced by potassium chloride (20 mM) in *in vitro* rat portal vein. As a result, the membrane potential reaches a level approximate to the K^+ equilibrium potential. Compound (10) showed the best activity out of all its analogs [25].



(10)

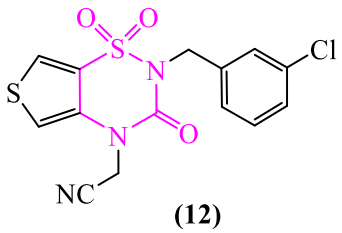
Anti-HIV Activity

Witvrouw M. and his colleague in 1998 synthesized a new group of 1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*] [1,2,4] thiadiazine family and screen them as anti-HIV. 2-(3-fluorobenzyl)-4-cyanomethylen-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine) (11) was the powerful derivative among the studied analogs which inhibit the replication of Human Immunodeficiency Virus (HIV) type 1 [HIV-1 (IIIB)] in MT-4 cells at 0.09 mM conc. [26].



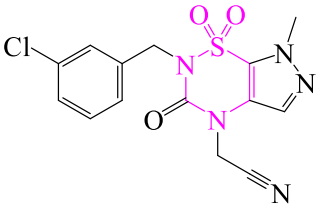
(11)

In the same previous year, Arranz E. synthesized and evaluated thieno[3,4-*e*] [1,2,4] thiadiazines for antiviral activity. The studied scaffolds act for a discovered type of non-nucleoside reverse transcriptase inhibitors (NNRTIs) which block HIV type 1 [HIV-1(IIIB)] replication selectively in MT-4 cells. The antiviral activity enhanced by *m*-halogen substitution of the *N*-2 benzyl group by one order of magnitude. Derivative (12) and (13) which have *N*-4 position a cyanomethyl and propyn-2-yl substituent, respectively, were discovered to be the most powerful derivative of the studied compounds [27].



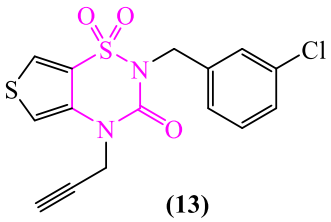
(12)

2-(*m*-Chlorobenzyl)-4-substituted-1, 1, 3-trioxo-2*H*, 4*H*-pyrazolo [4, 5-*e*] [1, 2, 4] thiadiazines were designed by Yan R-Z and co-workers in 2006 and estimated as anti-HIV replication in MT-4 cell cultures. Derivative **(14)** exhibit effect against cytopathicity induced by HIV-l with an IC_{50} value of 45.6 µM, but no compound show inhibitory action against HIV-2 [28].



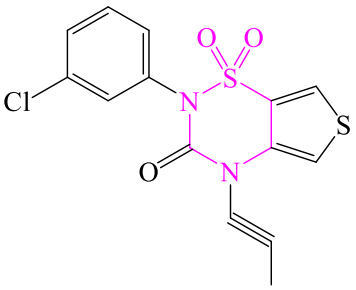
(14)

Quantitative structure-activity relationship (QSAR) study was developed targeting 1,1,3-trioxo [1,2,4] thiadiazine derivatives tracking for good anti-HIV drugs. The QSAR model revealed that the electronic descriptor (ionization potential), thermodynamic descriptors (molar refractivity), hydrogen bond donor and Hansen-polarity play a key role for the anti-HIV activities. The outcome of that study showed that compound (15) was the most potent derivative and these results may lead to design a powerful



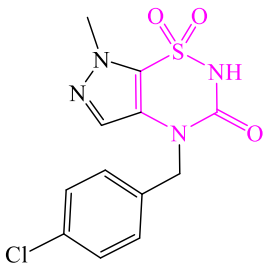
(13)

trioxothiadiazine analogues as anti-HIV compounds [29].



(15)

Additionally, new N4- substituted pyrazolo[4,5-*e*] [1,2,4] thiadiazines were synthesized by a regioselective deprotonation of Nitrogen atoms at four position which was performed by changing molar concentration of different alkyl halides and sodium hydride. Anti-HIV-1 analysis revealed some scaffolds were active as HIV-1 nonnucleoside reverse transcriptase inhibitors (HIV-1 NNRTIs). The anti-HIV-1 derivatives were evaluated *in vitro* against HIV-1 reverse transcriptase inhibition. The study outcomes indicate that just derivatives (16) and (17) appeared potent inhibitory activity on HIV-1 RT with IC_{50} values of 80 and 50 µmol L^{-1}, respectively [14].



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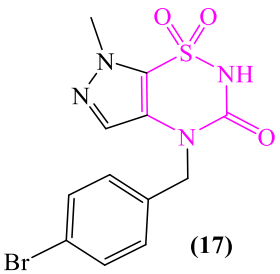
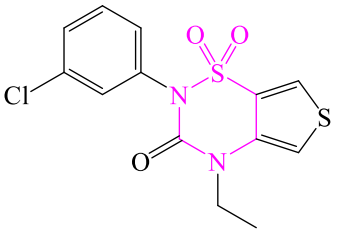


(17)

Moreover, Ravichandran V. 2009 have been performed three-dimensional (3D) QSAR studies to inhibit HIV-1 reverse transcriptase (RT). This study led to 2 reliable computational models and found compound (**18)** as the best encouraging derivative of HIV-1 (IIIB) replication inhibitor in MT-4 cells, that have been used as the alignment template [30].

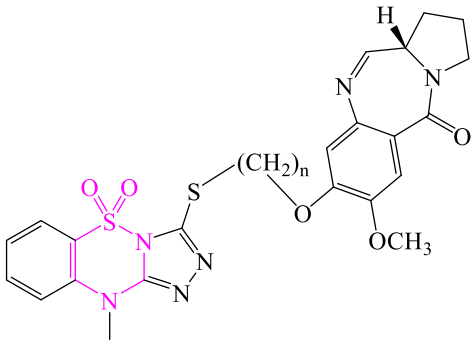


(18)

Anti-Cancer Activity

1,2,4-thiadiazine 1,1-dioxide, as other nucleus, were designed, synthesized as well as purified as anti-cancer agents, hopping to solve this intricate problem. Therefore, four publications discussed this issue between years 2008 to 2016.

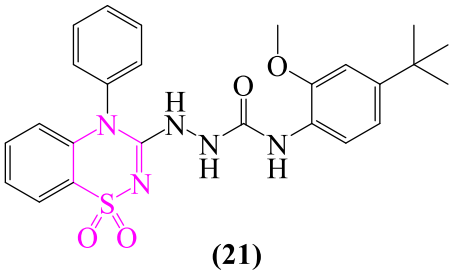
Kamal A. and his colleagues prepared in 2008 a series of pyrrolo benzodiazepine-triazolo benzo thiadiazine combines that were linked by various alkane bridges. These series have displayed a significant cytotoxicity versus the most of examined cell lines. Compounds (19) and (20) were specified as a promising candidate from this series because they exhibited a powerful activity versus seven human tumor cell lines. These compounds have substituted at position 10 with odd number of alkyl spacers (3 or 5) and exhibited better activities than their analogs which have even numbers. The CT-thermal denaturation studies of DNA of this series confirmed that the DNA helix melting point of the compound (20) was boosted by 2.6 °C after 36 h of incubation [31].



19, n=3; 20, n=5

(19, 20)

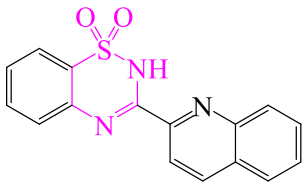
2-(1,1-dioxido-4-phenyl-4*H* benzo[*e*][1,2,4] thiadiazin-3-yl)-*N*-(4-methoxyphenyl) hydrazine carboxamide is another series which were intended and examined for its anticancer activity against different cancer cell lines containing prostate, colon, breast, ovary, and lung cancers by Kamal A. and his colleagues' team in 2011. All compounds of this series displayed respectable inhibitory activity against these cancer cell lines but derivative (21) was the best among them because of its two functional groups of *o*-methoxy and *m*-tertiary butyl of hydrazinocaboxamide analogs [32].



(21)

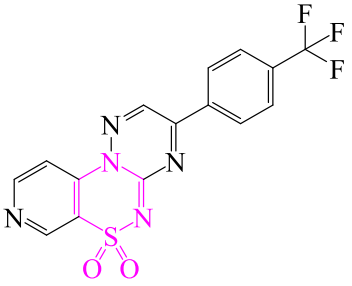
The condensation of heterocyclic methyl carbimidates with 4-chloropyridine-3-sulfonamide and 2-chlorobenzene sulfonamide resulted in the production of a novel series of 1,2,4-thiadiazine 1,1-dioxides. The anti-cancer and tuber cytostatic activities of the studied new scaffolds were estimated, and the outcomes revealed that eight members of this family could inhibit the expansion of non-small lung cancer, and renal cancer cell lines

while the compound (**22**) gave the highest activity among its parallel derivatives [7].



(22)

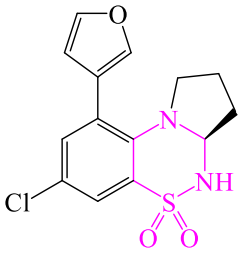
Sławi´nski J. synthesized in the year 2016 a novel system of heterocyclic pyrido [4,3-*e*] [1,2,4] triazino [3,2-*c*] [1,2,4] thiadiazine 1,1-dioxide ring which was the last series for such derivatives that was revealed by elemental analyses and spectroscopic techniques. The results confirmed that some of these derivatives displayed an acceptable anti-cancer activity against MCF-7 (breast cancer), HCT-116 (colon cancer), HeLa (cervical cancer) of the human cancer cell lines. Compound **(**23) displayed a distinguished activity and selectivity towards HCT-116 with IC_{50} value of 9 µM and also exhibited a structure-dependent moderate anti-cancer activity with IC_{50} = 25 µM against MCF-7, and HeLa as well [33].



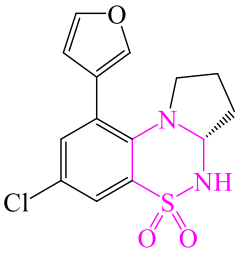
(23)

As AMPA receptors positive modulators

1,2,4-thiadiazine 1,1-dioxide moiety can play a key role as a modulator for the *α*-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) which belong to the ionotropic transmembrane receptors' family for glutamate (iGluRs). These receptors are involved in neurodegenerative diseases and the neurological disorders' pathologies. Carrozzo M. M. designed the compound 7-chloro-9-(furan-3-yl)-2,3,3a,4-tetrahydro-1*H*-benzo[*e*]pyrrolo[2,1-*c*] [1,2,4]thiadiazine 5,5-dioxide (±)-24 in 2014 to preserving AMPAR affinity and boost the stability towards the hydrolysis and the enantiomerization. The researchers promoted then the stereoselective synthesis to determine the single enantiomers of (±)-24, and use the X-ray diffraction spectroscopy to assign the absolute configuration of these enantiomers. According to the biological studies, a stereospecific interaction of (—)-(R)-24 with the AMPA receptor was suggested and the source of the stereospecific recognition with the receptor and the probable binding mode of (—)-(R)-24 was identified by performing some molecular modeling experiments on AMPAR GluA2 ligand binding domain [34].



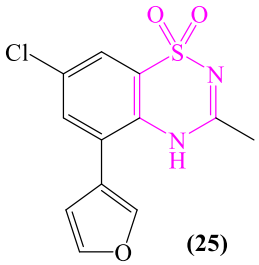
(S)-24



(R)-24

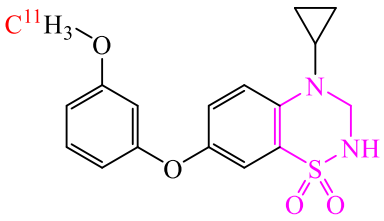
In another study, 7-Chloro-5-(furan-3-yl)-3-methyl-4*H*-benzo[*e*] [1,2,4]thiadiazine 1,1-dioxide (25) was synthesized in 2016 as a positive allosteric modulator of AMPA receptor by Citti C. and co-workers. Some experiments performed on the rat liver microsomes showed that the hepatic cytochrome P450 converted the parent compound [7-chloro-5-(3-furanyl)-3-methyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide] to the corresponding unsaturated derivative (25). The derivative (25) exhibited a significant activity compared to its parent compound when the patch-clamp **experiments were** carried out which confirmed by the molecular modeling studies. In addition,

the **(**25) increased the acetylcholine and serotonin levels in the hippocampus because it was able to cross the blood-brain barrier according to the mice cerebral microdialysis studies [35].



(25)

In 2020, a novel AMPAR PET (Positron Emission Tomography) tracer (26) was well-organized and synthesized by Chen J. and his team via a two-step strategy performed in a modified one-pot with a high molar activity and a high radiochemical yield. It was found that the radiochemical conversion was remarkably improved when the combination of Tetrabutylammonium hydroxide (TBAOH) in DMF was used. To explore the suitability of (26) as a potential PET probe for AMPAR imaging, a preliminary *in vivo* estimation was conducted. The binding specificity, brain uptake, *ex vivo* whole-body distribution, and clearance in rodents were accomplished to identify the pharmacokinetic profile of (26) [36].

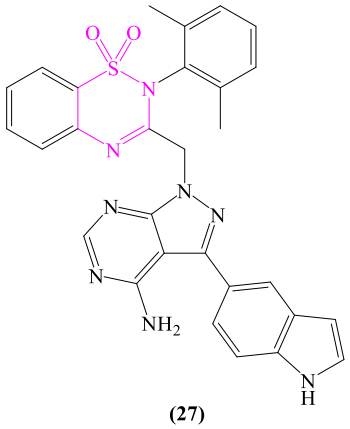


(26)

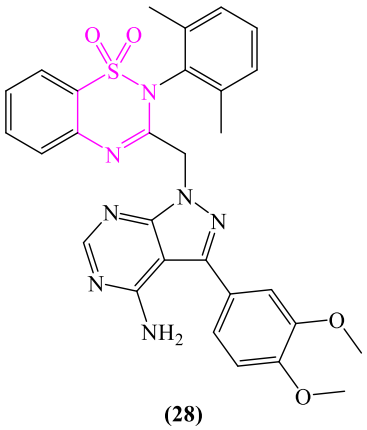
Miscellaneous Activities

As Phosphoinositide 3-kinases Inhibitors

Novel derivatives of 2H-benzo[e][1,2,4]thiadiazine 1,1-dioxide as PI3Kδ inhibitors series were synthesized in another study which included the compounds (27) and (28) with IC_{50} values of 266 and 217 nM, respectively as the highest potential analogs. Some derivatives in this novel series offered high decreasing in PI3Kδ inhibitory potency while surprisingly still maintained the high selectivity among the other PI3K isoforms. Compounds (27) and (28) significantly displayed the SU-DHL-6 cell proliferation due to their high PI3Kδ selectivity, and compound (28) offered 21-fold selective over PI3Kγ more than the other derivatives [37].



(27)

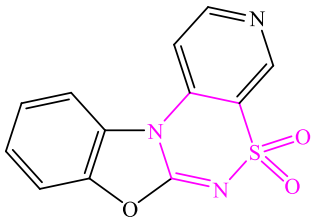


(28)

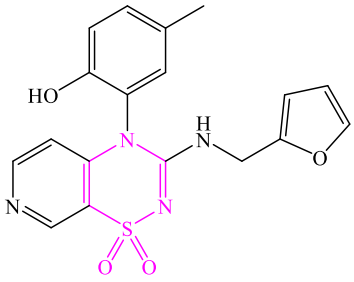
Antibacterial activity

The condensation of 3-methyl thiopyrido [4,3-*e*]-1,4,2-dithiazine 1,1-dioxide with 2-aminophenols or 2-aminothiophenol, and with 2-or 6-hydrazinoazines resulted in the production of two new series of 4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine derivatives (29) and (30), respectively. The X-ray diffraction, spectral data, and elemental analysis techniques were performed to confirm the structures of these derivatives. Furthermore, in the full NCI 60 cell panel

at a single dose (10 μM) from the synthesized compounds, the preliminary *in vitro* anticancer assay was conducted, and the results confirmed that the most potent among all derivatives were compounds (29) and (30) [13].



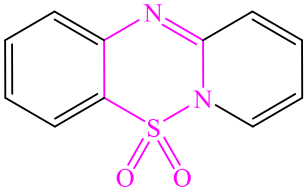
(29)



(30)

Anti-inflammatory Activity

In 2019 one-pot, telescopic approach for the chemoselective synthesis of benzo[*e*]pyrido/ pyrazino/ pyridazino [1,2-*b*] [1,2,4] thiadiazine dioxides derivatives was developed by Padmaja. The ability to bind the macromolecules and the potency as anti-inflammatory agent for the new synthesized compounds were estimated, and these derivatives considered as potent candidates for biomolecular probes while compound (31) was chosen as the best one. After many investigations on the unique heterocyclic molecules, it was recommended that these derivatives might be a good candidates for the drug discovery applications [38].



(31)

Conclusions

In this review and in spite of deficiency of biological applications of 1,2,4-thiadiazine dioxides scaffolds, it can be concluded that researchers synthesize this scaffold and study their diverse biological applications especially as channel openers since their structures similar to diazoxide and pinacidil drugs. Other biological applications were studied as well such as their anti-HIV activity, anti-cancer activity, anti-tuberculosis activity, as AMPA receptors positive modulators, enzymes inhibitor, antimicrobial, and anti-inflammatory. More studies needed on this nucleus to synthesis more derivatives with more potent biological activities as potential drugs.

Acknowledgments

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References

1- Hasan H. A., Abdulmalek E., Saleh A. T., Abdul Rahman M. B., Sharri K., Bohari M. Y., and Chan K.W. Synthesis of novel 6-substituted-5,6-Dihydrobenzo[4,5] Imidazo[1,2- c] quinazoline compounds and evaluation of their properties. J. Mol. Struct. 2019. Vol. 1193. Pp: 482–494.

2- Hasan H. A., Raoof S. S., and Abd Razik B. M. Synthesis, characterization and molecular docking simulation of thioxothiazolidin-4-one derivatives as acetylcholinesterase inhibitors. Syst. Rev. Pharm. 2020. Vol. 11. Pp: 1920–1926.

3- Hasan H. A., Abdulmalek E., Abdul Rahman M. B., Sharri K., Bohari M. Y., and Chan K. W. Microwave synthesis, crystal structure, antioxidant, and antimicrobial study

of new 6-heptyl-5,6-dihydrobenzo[4,5]imidazo[1,2-c] quinazoline compound. Chem. Cent. J. 2018. Vol. 12. Pp: 1–15.

4- Khan A. K. Synthesis, Identification and Anti-candidaProperties of Some NewBis (Five, Six, Seven-membered Heterocycles) AttachedPyrrole Rings. AJPS, 2017. Vol. 17, No.1. Pp:176-191.

5- Al-Smaism R. F., Raauf A. M. R., Abd Razik B. M. Hala A.M. Rasheed. Synthesis, Characterization and Antimicrobial Activityof 3-substituted Benzo[4,5]thiazolo[2,3-c][1,2,4]triazole. AJPS, 2013. Vol. 13, No.2. Pp: 9-15.

6- Pascal de T., Raogo O., Leon D., Fabian S., Stephane B., Jean-M.D., Jacques D. and Bernard P. Synthesis and Structural Studies of 3-Alkylamino-pyrido[4,3-e]-l,2,4-thiadiazine l,l- dioxides: a New Class of Heterocyclic Compounds with Therapeutical Promises. Tetrahedron. 1999. Vol. 55. Pp: 5419–5432.

7- Katarzyna G., Henryk F., Jarosław S., Ewa A.-K., and Agnieszka N. Synthesis and biological activity of novel 3-heteroaryl-2H-pyrido[4,3-e][1, 2,4]thiadiazine and 3-heteroaryl-2H-benzo [e][1,2,4] thiadiazine 1,1-dioxides. Monatshefte fur Chemie. 2013. Vol. 144. Pp: 1197–1203.

8- Peng Z., Renzhang Y., Xinyong L., Christophe P., Myriam W., Erik De C., Molina M. T., and Vega S. Synthesis and anti-HIV activity of novel 2,4-disubstituted-7-methyl-1,1,3- trioxo-2H,4H-pyrazolo[4,5-e][1,2,4]thiadiazine derivatives. Drug Discov. Ther. 2011.Vol. 5. Pp: 279–285.

9- Kumar G. R., Swarnayu B., Ramesh B., Sridhar B., and Basireddy V. S. R. Oxidative Annulation of 3-Aryl-2H-benzo [e][1,2,4]thiadiazine-1,1-dioxides with Aryl Aldehydes: An Easy Access to Hydroxyisoindolo [1,2-b] benzothiadiazinedioxide Scaffolds. European J. Org. Chem. 2020. Vol. 2020. Pp: 923–931.

10- Ahmed K., Srikanth Y. V. V., Ashraf M., Khan N. A. M., Thokhir B. S., Shasi V. K., Nitasha S. and Saxena A. K. Synthesis and Anticancer Activities of New Benzothiadiazinyl Hydrazine- carboxamides and Anilino [1 , 2 , 4] triazolo [1 , 5- b][1 , 2 , 4] thiadiazine 5 , 5-diones. Med. Chem. 2011. Vol. 7. Pp: 165–172.

11- Vega S., Arranz M. E. and Vicente J. A. Synthesis of Oxazolo[3,2-b] hetero[1,2,4] thiadiazine S,S-Dioxides. J. Heterocycl. Chem. 2005. Vol. 42. Pp: 755–761.

12- Xin Y. L., Ren Z. Y., Nian G. C., and Wen F. X. Regioselective synthesis and anti-HIV activity of the novel 2- and 4-substituted pyrazolo [4 , 5- e][1 , 2 , 4] thiadiazines. Chinese Chem. Lett. 2007. Vol. 18 (2). Pp: 137–140.

13- Cyrille L., David D., Alain R. and Jean C. M. Synthesis of novel 6,7-dihydrothiazolo[3,2-b]-1,2,4-thiadiazine 1,1-dioxides. Tetrahedron Lett. 2002. Vol. 43. Pp: 4099–4101.

14- Wang D., Liu W., Yi F., Zhao Y. and Chen J. Palladium-catalyzed direct C-H arylation of 3-aryl-2H-benzo [1,2,4]thiadiazine 1,1-dioxides: An efficient strategy to the synthesis of benzothiadiazine-1,1-dioxide derivatives. Org. Biomol. Chem. 2016. Vol. 14. Pp: 1921–1924.

15- Zdzisław B., Jarosław S., Anna K., Ewa K., and Maria G. Application of 3-Methylthiopyrido [4,3-e]-1,4,2-dithiazine 1,1-Dioxide to the Synthesis of Novel Series of 4H-Pyrido[4,3-e]- 1,2,4- thiadiazine Derivatives with Potential Biological Activity. J. Heterocycl. Chem. 2009. Vol. 46. Pp: 1396–1403.

16- Vega S., Arranz M. E. , and Vicente J. A. Synthesis of new hetero[1,2,4]thiadiazin-3-one S,S-dioxides and Oxazolo[3,2-b]hetero[1,2,4]thiadiazine S,S-dioxides as potential psychotropic

drugs. J. Heterocycl. Chem. 2005. Vol. 42. Pp: 763–773.

17- Pascal de T., Khelili S., Raogo Ouedraogo R., Somers F., Boverie S., Dupont L., Fontaine J., Antoine M. -H., Delarge J., Philippe L., and Pirotte B. 3-Alkyl amino- pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxides as Potent KATP-Channel Activators: Structural Study and Influence of Stereochemistry. pharm. Pharmacol. Commun. 2010. Vol. 5. Pp: 195–198.

18- Bernard P., Pascal de T., Philippe L., Antoine M. -H., Jeanine F., Bernard M., Marc S., Dupont L., Herchuelz A., and Delarge J. 3-(Alkyl amino) -IH-pyrido[4,3-e] -l,2,4-thiadiazine 1,1-Dioxides as Powerful Inhibitors of Insulin Release from Rat Pancreatic B-Cells: A New Class of Potassium Channel Openers? J. Med. Chem. 1993. Vol. 36. Pp: 3211–3213.

19- Bernard P., Antoine M.-H., Pascal de T., Hermann M., Herchuelz A., Delarge J. and Philippe L. A pyridothiadiazine (BPDZ 44) as a new and potent activator of ATP-sensitive K+ channels. Biochem. Pharmacol. 1994. Vol. 47. Pp: 1381–1386.

20- Pascal de T., Bernard P., Philippe L., Jeanine F., Le´on D., Antoine M.-H., Ouedraogo R., Khelili S., Maggetto C., Masereel B., Ousmane D., Podona T., and Delarge J. 3- and 4-substituted 4H-pyrido[4,3-e]-1,2,4-thiadiazme 1,1-dioxides as potassium channel openers: Synthesis, pharmacological evaluation, and structure-activity relationships. J. Med. Chem. 39. 937–948 (1996).

21- Khelili S., Pascal de T., Philippe L., Marianne F., Antoine M.-H., Ouedraogo R., Leon D., Jeanine F., Apostolos F., Gerard L., Delarge J., and Bernard P. Preparation and pharmacological evaluation of the R- and S-enantiomers of 3-(2'-butylamino)-4H- and 3-(3'-methyl-2'-butylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide, two tissue selective ATP-sensitive potassium channel openers. Bioorganic Med. Chem. 1999. Vol. 7. Pp: 1513–1520.

22- Bernard P., Ouedraogo R., Pascal de T., Khelili S., Fabian S., Ste´phane B., Le´on D., Jeanine F., Jacques D., and Philippe L. 3-alkylamino-4H-pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxides structurally related to diazoxide and pinacidil as potassium channel openers acting on vascular smooth muscle cells: Design, synthesis, and pharmacological evaluation. J. Med. Chem. 2000. Vol. 43. Pp: 1456–1466.

23- Nielsen F. E., Bodvarsdottir T. B., Worsaae A., MacKay P., Stidsen C. E., Boonen H. C. M., Pridal L., Arkhammar P. O. G., Philip W., Ynddal L., Junager F., Dragsted N., Tagmose T. M., Mogensen J. P., Anette K., Treppendahl S. P., and Hansen J. B.; 6-Chloro-3-alkylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-Dioxide Derivatives Potently and Selectively Activate ATP Sensitive Potassium Channels of Pancreatic B-Cells. J. Med. Chem. 2002. Vol. 45. Pp: 4171–4187.

24- Nielsen F. E., Søren E., Anette F. J., Lars Y., Bodvarsdottir T. B., Stidsen C. E., Worsaae A., Boonen H. C. M., Arkhammar P. O. G., Tinna F., Philip W., Hanne T. K., and Hansen J. B. New 3-alkylamino-4H-thieno-1,2,4-thiadiazine 1,1-dioxide derivatives activate ATP-sensitive potassium channels of pancreatic beta cells. J. Med. Chem. 2006. Vol. 49. Pp: 4127–4139.

25- Arranz M. E., Juan A. D., Salvador V., Manuel C.-T., Francisco O., Ignasi C., Jesús L., Fernandez A. G. Synthesis and pharmacological evaluation of 2,3-dihydro-3-oxo-4H-thieno[3,4-e][1,2,4]thiadiazine 1,1-dioxides as voltage-dependent calcium channel blockers. Eur. J. Med. Chem. 2000. Vol. 35. Pp: 751–759.

26- Witvrouw M., Arranz M. E., Pannecouque C., Declercq R., Jonckheere H., Schmit J.C., Vandamme A. M., Diaz J. A., Ingate S. T. Desmyter J., Esnouf R., Merrvelt L. V., Vega S., Balzarini J., and Clercq E. De. 1,1,3-trioxo-2H,4H-thieno[3,4-e][1,2,4]thiadiazine (TTD) derivatives: A new class of nonnucleoside human immunodeficiency virus type 1 (HIV-1) reverse transcriptase inhibitors with anti-HIV-1 activity. Antimicrob. Agents Chemother. 1998. Vol. 42. Pp: 618–623.

27- Arranz M. E., Juan A. D., Simon T. I., Witvrouw M., Pannecouque C., Balzarini J., Clercq E. De, and Vega S. Novel 1,1,3-trioxo-2H,4H-thieno [3,4-e] [1,2,4] thiadiazine derivatives as non-nucleoside reverse transcriptase inhibitors that inhibit human immunodeficiency virus type 1 replication. J. Med. Chem. 1998. Vol. 41. Pp: 4109–4117.

28- Ren -Z. Y., Xin-Y. L., Wen -F. X., Christophe P., Witvrouw M., and Clercq E. De. Synthesis and Anti-HIV Evaluation of the Novel 2-(m-Chlo-robenzyl)-4-substituted-7-methyl-1, 1, 3-trioxo-pyrazolo[4, 5-e] [1, 2, 4]thiadiazines. Arch Pharm Res. 2006. Vol 29. Pp: 957–962.

29- Ravichandran V., Mourya V. K., Agrawal R. K. QSAR study of novel 1,1,3-trioxo[1,2,4]-thiadiazine (TTDs) analogues as potent anti-HIV agents. ARKIVOC. 2007. Vol. 2007(14). Pp: 204–212.

30- Ravichandran V., Kumer P. B., Sundaram S., and Ram K. A. Predicting anti-HIV activity of 1,1,3-trioxo[1,2,4]-thiadiazine (TTD) derivatives: 3D QSAR approach. Med. Chem. Res. 2009. Vol. 18. Pp: 511–522.

31- Kamal A., Naseer Khan M. A., Srikanth Y. V. V., Srinivasa R. K., Aarti J., Subrata S., Nisha K., and Surekha Z. Synthesis, DNA-binding ability and evaluation of antitumour activity of triazolo[1,2,4]benzothiadiazine linked pyrrolo[2,1-c][1,4]benzodiazepine conjugates. Bioorganic Med. Chem. 2008. Vol. 16. Pp: 7804–7810.

32- Kamal A., Srikanth Y. V. V., Ashraf Md., Naseer Khan M. A., Thokhir B. S., Shasi V. K., Nitasha S. and Saxena A. K. Synthesis and Anticancer Activities of New Benzothiadiazinyl Hydrazine- carboxamides and Anilino [1 , 2 , 4] triazolo [1 , 5- b][1 , 2 , 4] thiadiazine 5 , 5-diones. Med. Chem. 2011. Vol. 7. Pp:165–172.

33- Jarosław S., Aleksandra G., Beata Z. and Anna K. Synthesis of novel pyrido[4,3-e][1,2,4] triazino[3,2-c][1,2,4] thiadiazine 6,6-dioxide derivatives with potential anticancer activity. Molecules. 2016. Vol. 21(1). Pp: 1–16.

34- Marina M. C., Umberto M. B., Giuseppe C., Giulia P., Federica R., Aurelia F., Serena P., Cinzia C., Krzysztof J., Daniela B., Carlo P., Luigino T. Design, stereoselective synthesis, configurational stability and biological activity of 7-chloro-9-(furan-3-yl)-2,3,3a,4-tetrahydro-1H-benzo[e]pyrrolo[2,1-c][1,2,4]thiadiazine 5,5-dioxide. Bioorganic Med. Chem. 2014. Vol. 22. Pp: 4667–4676.

35- Cinzia C., Umberto M. B., Giuseppe C., Krzysztof J., Natalia S., Giulia P., Federica R., Giuseppe C., Daniela B., Carlo P., Luigino T., and Michele Z. 7-Chloro-5-(furan-3-yl)-3-methyl-4H-benzo[e][1,2,4]thiadiazine 1,1-Dioxide as Positive Allosteric Modulator of α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) Receptor. The End of the Unsaturated-Inactive Paradigm? ACS Chem. Neurosci. 2016. Vol. 7. Pp: 149–160.

36- Jiahui C., Jiefeng G., Jiyun S., Zhen C., Hualong F., Jian R., Xiaoyun D., Jingjie S., Jian G., Tuo S., Lee C.,

Wang L., Hao X., Steven H. L. Radiosynthesis and preliminary evaluation of 11C-labeled 4-cyclopropyl-7-(3-methoxyphenoxy)-3,4-dihydro-2H-benzo[e] [1,2,4] thiadiazine 1,1-dioxide for PET imaging AMPA receptors. Tetrahedron Lett. 2020. Vol. 61. P: 151635.

37- Ya-Ping G., Long-Q. T., Tong-S. L. and Zhao-P. L. Synthesis and Evaluation of Novel 2H-Benzo[e]-[1,2,4]thiadiazine 1,1-Dioxide Derivatives as PI3Kδ Inhibitors. Molecules. 2019. Vol. 24. Pp: 1–14.

38- Ramsingh D. P., Musuvathi M. B., and Kaushik C. One-Pot, Telescopic Approach for the Chemoselective Synthesis of Substituted Benzo[e]pyrido/pyrazino/pyridazino[1,2- b][1,2,4] thiadiazine dioxides and Their Significance in Biological Systems. J. Org. Chem. 2019. Vol. 84. Pp: 11382–11390.