

Synthesis and pharmaceutical applications of Oxazine compounds derived from Pyronic, Salicylic, Anthranilic acids and Phenols

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International Journal of Science and Research Archive, 2021, 02(02), 074–086

Publication history: Received on 05 April 2021; revised on 14 April 2021; accepted on 17 April 2021

Article DOI: <https://doi.org/10.30574/ijrsra.2021.2.2.0250>

Abstract

It is well known from FDA reports that More than 75% of the heterocyclic compounds are drugs and 90 of heterocyclic compounds are cancer drugs. The nitrogen-based heterocycles occupy an exclusive position as a valuable source of therapeutic agents in medicinal chemistry. Most drugs approved by the FDA and currently available in the market are nitrogen-containing heterocyclic moieties, More over heterocyclic compounds are important class of organic chemistry due to their widely spread in nature. Also there are many route for their action and many mechanistic pathways for their preparation and different metabolic actions. This comes from the easily building or removal of any functional group within the molecules. Changing just on group cause to change the metabolic pathway of the drug action and site of attack of the desired target accordingly. This great characteristic value make them much more important in drug discovery programs of many researchers and also encouraged us and drew attentions of other researchers to develop new ways for their synthesis. As a result different pharmacological and medical applications. Oxazie compounds are sub branch of heterocyclic compounds. These compounds having two hetero atoms, Oxygen and nitrogen within their structures make them much more important toward therapeutic studies. We are here in our investigation will focus on the methodologies and the therapeutic action of the titled compounds as well as other various applications.

Keywords: Synthesis; Application; Pharmaceutical; Pyronic; Salicylic anthranilic acids and phenols

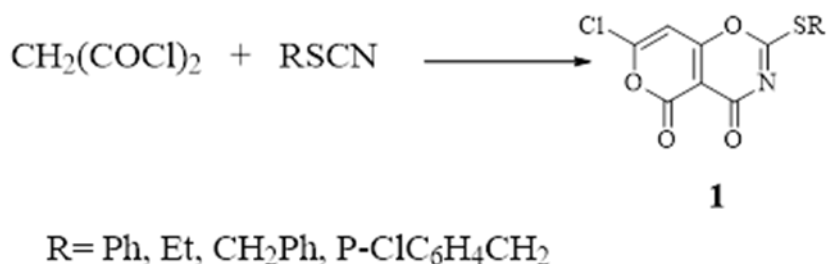
Graphical abstract



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1. Introduction

The first time that pyrano oxazine compounds were synthesized in 1952 during the work of Elvidge, Al-rawi et-als [1-10] from the reaction of pyronic acid with thiocyanate, isothiocyanate or the self-condensation of malonyl chloride with the above thiocyanate or isothiocyanate. As it was shown below:

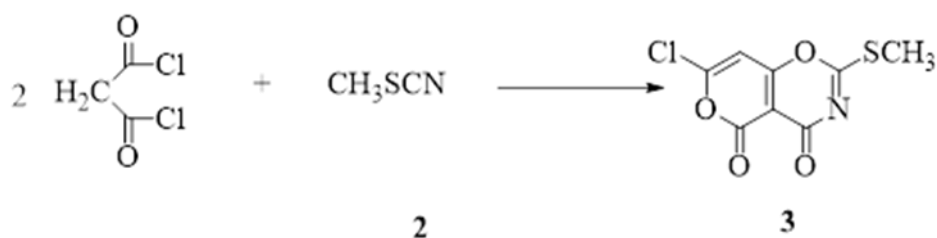


Scheme 1 Pyrano oxazine formation

Some of the synthesized compounds have shown anti-microbial activity against gm +ev and gm -ev bacteria and fungi [11-16].

Other researches were studied the reaction of oxazines with different primarily amine forming the corresponding diazine compounds. Some other researchers have prepared pyronooxazines also from the self-condensation of malonyl chloride with thiocyanate but here the product of the pyronooxazines was reacted with amino acid esters and results into the formation of biologically active compounds toward some microorganisms [17,18].

In 2000 Al-ajely and Al-Abachi [19] have prepared the oxazino compound 7-chloro-2-methyl thio-2-ethyl carbazato-2,3-di hydropayrono [3,4-e[1,3] oxaine-4,5-dion (compound 3) which was the result of the reaction of the ethyl carbazate with compound (2). Compound (2) itself was prepared from the self-condensation of methyl thiocyanate with malonyl chloride.



Scheme 2 Self-condensation of methyl thiocyanate with malonyl chloride

This compound showed very important screening effect against 8 types of cancer of different cell lines with killing efficiency between 98-100 % of the cancer cells. The compound is effective in killing cancer cells of throat and lymph types NCI H522, NCI 1322M, NCI H23, NCI H226, HOP 62, A549ATCC and colon cancer of types KM12, HT29, HCT 15, HCT 116, HCC for 100 % killing efficiency. Also showed nearly 100 % killing skin type cancer MALME 3M. This compound was also found to be effective toward ovary cancer cell lines for the following types OVCAR-8, OVCAR-4, OVCAR-3 and IGROVI-1. The above compound was also found effectively killing the cancer cells of central nervous system types SNB-95, SF-295 100 %. The compound showed 99-100 % killing of kidney cancer cells of types UO-31, ACHN-7860. It works also against prostate cancer type PC-3 with 100 % killing. Finally, this compound showed 100% killing of breast cancer MCF-7.

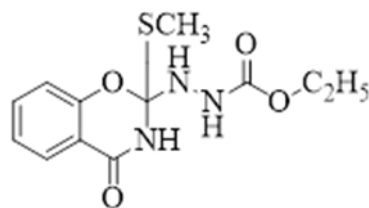


Figure 1 ethyl 2-(2-((methylthio)methyl)-4-oxo-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-yl)hydrazine-1-carboxylate

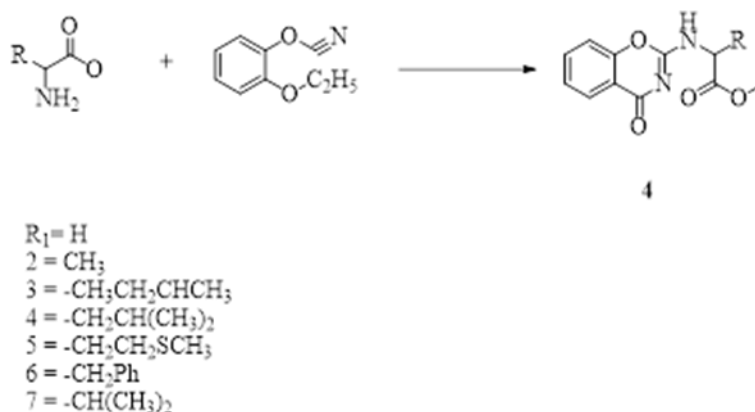
In 2007, Al-ajely and basher have synthesized some 1,3-oxazine from malonyl chloride from methyl and benzyle thiocyanate and reacted the resulted product with some amino acid esters and their hydrazides [20].

In the same year the above researchers were studied the biological activity of some amino acid esters and their hydrazide against gm +ve and gm -ev bacteria [21].

1.1. Oxazine compounds derived from salicylic acid and its derivatives

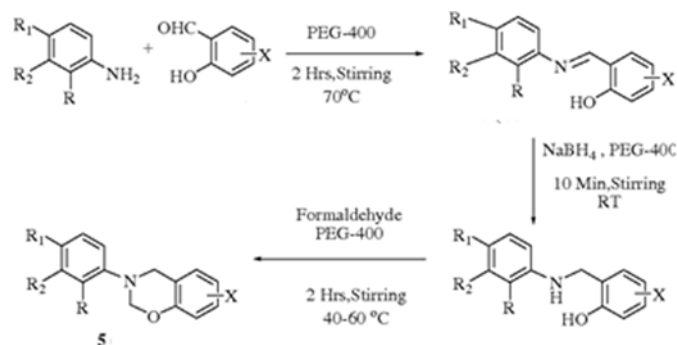
Zilong Tang and his co-workers have prepared N-alkyl-2-aryl benzooxazine from the reaction of benaldehyde with alkyl amines then the formed shiff bases were reduced by sodium borohydride into the corresponding amine then cyclized this amine using TMSCl as catalyst in to the 1,3-oxazine compound. These compounds were proved to have anti-fungal activities against five strains of phytopathogenic fungi [22].

In 2013 Al-ajely has prepared some oxazine compounds from the reaction of 2-ethyl phenyl cyanate with some amino acid esters (compounds 4a-j). The amino acid ester derivatives of some of these oxazines were found to have (anti-platelet) activity [23].



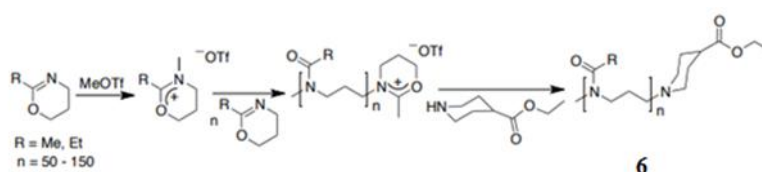
Scheme 3 Synthesis of oxazine derivatives

Al-rawi and Tyson have prepared substituted 1,3-benzooxazine-2-thion compounds from the reaction of either substituted salicylic acid with dithiocyano triphenyl phosphen or from 2 ethyl substituted phenyl cyanate with amines. The prepared 2-amino-1,3-benzaxazine and the thion compounds were screened against gm +ve and gm -ve bacteria. They showed significant effects toward these types of bacteria [24]. In 2014 Rahul and his coworkers have prepared , dihydro-2H-benzo[1,3]oxazine from the reaction of salicylaldehyde and some substituted amines then reduction with NaBH₄ and cyclization to give the oxazine compounds as shown below in scheme 4. They evaluated benzo[1,3]oxazine derivatives as growth inhibitors of *M. tuberculosis*. Some of the synthesized compounds showed promising activity against *M. tuberculosis* when compared with currently used drugs such as Refampicin and Ethambutol [25].



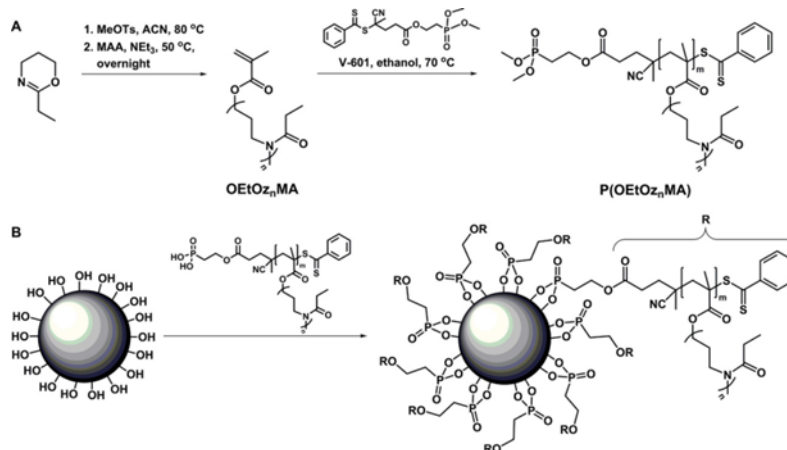
Scheme 4 Formation of dihydro-2H-benzo[1,3]oxazine

Zuzana Kronekova et-al have synthesized 2-alkyl-2-oxazine monomers and have polymerized this oxazine into water soluble poly(2-substituted-5,6-dihydro-4H-1,3-oxazine). As shown below:



Scheme 5 Schematic representation of the synthesis and structure of poly(2-oxazine)s.

This polymer was evaluated with respect to their cytotoxicity against 3T3 mouse fibroblasts. The study revealed that there is no toxic effect which was tested for mice [26]. Some other research have used this polymer in Nano medicine [27].



Scheme 6 Synthesis of poly(oligo(2-ethyl-2-oxazine) (A) methacrylate) (P(OEtOznMA)) by the reaction of CROP with RAFT polymerization using phosphonate as transfer agent (CTA); (B) by grafting of phosphonic acid.

1.2. Oxazine compounds drives from anthranilic acid and its derivatives

There are a lot of methods in the literature concerning the synthesis of oxazine compounds from anthranilic acid by ring closure either by acetic anhydride[28,29] or chloro acetyl chloride [30] or succinic anhydride[31] or alkyl chloro acetate[32] and ethyl ester derivatives[33] such as cynao ethyl ester. There were also other methods found in the literature for synthesizing of 1,3-oxazine other than the mentioned above [34-49] some of them have antimicrobial activities among other than anthranilic acid precursors for oxazine synthesis are the following: Amidosalysilate [50,51]. These compounds were cyclized either by tosyl chloride, isothiocyanate, pyridine and chloroformate [52-55] and Vilsmeier-Haack reaction [56,57]. The other derivatives of anthranilic acid is isocyanate which upon cyclization affords 1,3-oxazines [58-61]. It was also found that the anthranilic acid isocyanate derivatives interacts with amino acid esters affording a biological active oxazine compounds. The water solution of these compounds showed HLE and human

sputum elastase activities [62-64]. The other Miscellaneous oxazine precursors are iminophosphorane alkyl phenyl esters [65], N-benzenesulfonyl anthranilic acid [66], cyclization by refluxing of orthothioamidobenzoic acid using t-butyl benzene [67].

The above research works were started in nineteenth century which encouraged many researches to develop new methodologies for the synthesis of these compounds Irani and Nikpour have reported the synthesis of some oxazine from anthranilic acid derivatives and some aldehydes using phenyl isocyanate in good and high purity[68]. In 2011 Anilkumar. R. has reported the synthesis and the pharmacological activities of some oxazine compounds derived from anthranilic acid and revealed that these compounds have anti-inflammatory effect [69]. Osman et-al. Have synthesized some oxazine containing sulphonate moiety from anthranilic acid Their compounds showed a remarkable biological activity toward Bacillus Thuringensis and Klebsiella Pneumonia [70] Mohamed and Ahmed have used anthranilic precursors for preparing 4-oxo-2-phenylquinazolines from the corresponding 3,1-oxazines. These compounds were tested for their in vitro antimicrobial activity against the Gram-positive bacteria, Staphylococcus aureus and Bacillus subtilis, the Gram negative bacteria, Escherichia coli and Klebsiella pneumonia the synthesized compounds showed higher activity toward gm.+ve than gm.-ve one[71]. James D. Patronea and his team have discovered an anthranilic acid derivative 4-Bromo-2-(3-(N-(3,4-dichlorophenyl) sulfamoyl)-4-methyl benzamido) benzoic acid to inhibit the Replication of Protein A (RPA) which can specifically disrupt proten- proten interactions these interactions is important for validating RPA as a cancer target [72]. Figure 2

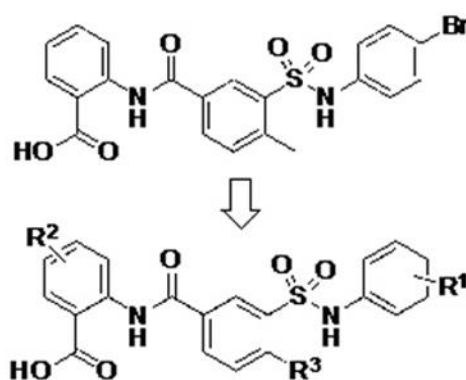


Figure 2 4-Bromo-2-(3-(N-(3,4-dichlorophenyl) sulfamoyl)-4-methyl benzamido) benzoic acid

Guhufuran in her thesis has prepared some aryloxy benzoxazines and studied their biological activities against some microorganism, The study have showed excellent screening effects against the studied organisms[73,74].

1.3. Oxazines Drives from Phenoles

In 1962, researches have study the synthesis of 3,1-oxazine-2-thions and their cytotoxic activity against amobarbital ascites sarcoma and Ehrlich ascites carcinoma. Some of the prepared compounds (in vivo study) showed a good screening activity of the last type of tumor [75]. The years after some researchers have developed another methodology for the synthesis and the medical application of this type of compound for example the work of Zuhail et-al. [76, 77]. Zheng and co-workers have synthesized the oxazines from the mentioned references using microwave technique for their preparation and screened them against some fungi [78]. In 2014 Mathew et-al have synthesized cromeno oxazine derivatives from the reaction of hydroxyl cromo derivatives with 7-hydroxy-4-methyl-2-thiocoumarin. They found that these compounds were active against in both in vivo and vitro anti-bacterial effect [79]. Benzekri et-al. Have developed new catalyst for the cyclization of phenols in to oxazine using snail shell. [80] In the same year, Pradeep K. et-al. have synthesized 1,3-oxazine compounds in water using ultrasound technique. The prepared compounds were used for the synthesis of anticancer indole, Cephalandole A [81]. as shown below:



Scheme 7 Synthetic pathway for functionalized 2-oxo-benzo[1,4]oxazines

Dhafer and his co-workers have reviewed the synthesis and anti-microbial, antitubercular, ntioxidant, anticancer and anti-inflammatory effects of these synthesized oxazines [82]. Çigdem Özen et-al. Have studied substituted 1,4-oxazine as DNA topoisomerase I inhibitors which might acts as a novel constructs for future anticancer agent designs [83].

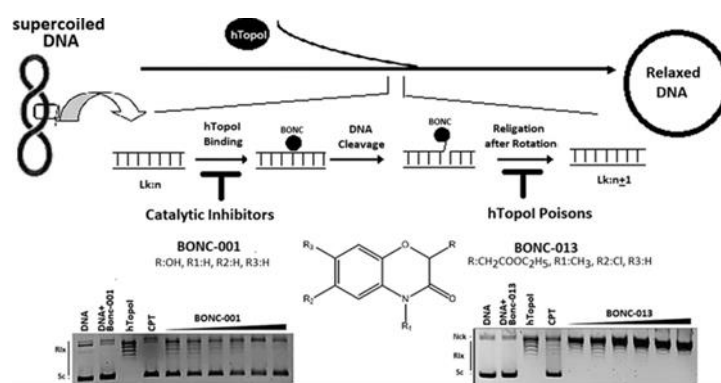


Figure 3 Shows the action of oxazine compound toward the DNA preparing strands.

Poly (2-oxazine)s of phenolic precursors were studied by Ondrej and were found to be used as drug carriers alternative to PEG and poly(N-hydroxypropylmethacrylamide) which are context of current polymer therapeutics research due to their high synthetic modularity [84].

1.4. Oxazine as industrial dyes and drugs

1,4-oxazine was found to be used in dyeing industry and also these dyes were found to be active against the growth of the skin cancer this comes from the research work of Margaret et-al. They studied the application of oxazine Nile blue dye for treatment of skin cancer of mice. It was found that significant retardation of their growth among fifty five of oxazine dyes, 17 were phenoxazines and 38 were benzo[a] phenoxazines were studied for the above purposes [85].

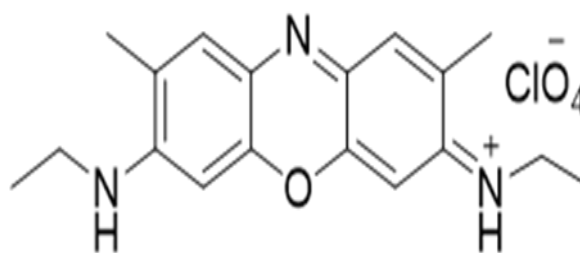
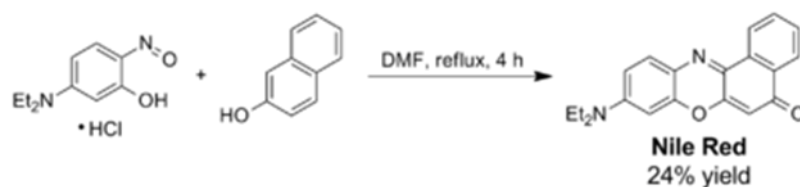


Figure 4 Nile blue dye

Gallocyanin is a red pigment can be prepared from the hydrolysis of nile blue with sulfuric acid or interaction of nitrosophenols with β -naphthol as shown below:

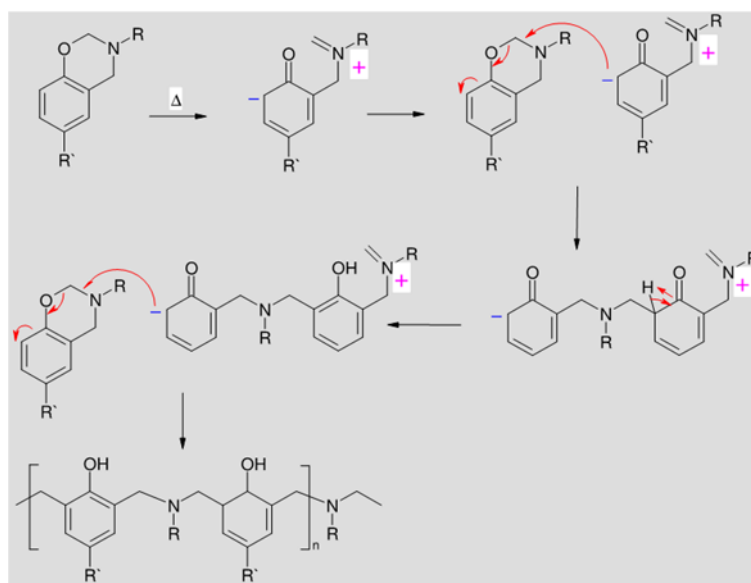


Scheme 8 The synthesis of nile red from β -naphthol

This pigment is used as a membrane dye which is essential to distinguish the internal cells [86]. Resazurin is also an oxazine dye with blue into purple in color which has redox sensitive to PH. So it is used for enzymatic and cellular assay in microbiological applications [87,88]. Jiney Jose et-al have prepared two benzophenoxazine derivatives. these dyes were used to clone type nine cells and which were selectively adopted for staining of both golgi and mitochondria [89]. It was found in the literature that Rhodamine dyes exhibit anti-malarial activity compared to chloroquine [90]. Oxazine dye due to their fluorescence behavior also used for the measurements of in vitro single-molecule for imaging super-resolution [91].

1.5. Oxazine Polymers, their utility as drug

Oxazine compounds were polymerize on heating by ring opening mechanism as shown in scheme (9) below:



Scheme 9 The ring opening polymerization of 1, 3-oxazines

Although these polymer have higher thermal thermoplastic stability especially for benzoxazines prepared from bis phenol A and aromatic and aromatic amine [92]. Amal F. Jaffar has studied the synthesis of polyoxazine blend with the oxazine dye. She also studied the third order non-linear optical properties which has medical applications [93]. Poly oxazine Nanoparticles of a drug-loaded was studied by Palanikumar [94] This polymer consist of polylactic-co-glycolic acid (PLGA) center which is covalently covered with a crosslinked bovine serum of albumin (BSA). This polymer showed successful to the targeting of anti-cancer chemotherapeutic drug delivery systems [95]. Zivani et-al have reviewed the synthesis of poly (2-oxazine POz) and their medical application and its co-polymers [96]. Young et-al have investigate the thermo sensitive character of pole oxazines as a smart material for various bio applications such as surfactant, hydrogel and some other properties of these polymers [97]. Anna and Robert have reviewed the recent concepts of using both poly -oxazolone (PAox) and poly oxazines (PAOzi) and their therapeutic effect in their impact in drug delivery system as drug carriers [98]. Recently Zivani Varanaraja and co- workers have also reviewed the synthesis and medical applications of poly oxazines up dating their physical properties [99]. Anna Zahoranová and Robert Luxenhofer have reported the implications of poly oxazolone and poly oxazine polymers as a non-covalent drug delivery system [100]. Ondrej and co-orkers have copolymerize pole oxazoline and poly oxazine which showed opposite site of polymerization rather the ordinary homo polymerization way. This one step polymerization has proved to offer a stimulation for nonionic surfactant which is used for many applications [101].

1.6. Oxazine as a commercial drug [102]

Table 1 below showing the oxazine compounds used as commercial drug their name and their actions:

Table 1 The oxazine drugs.

DRUG	DRUG DESCRIPTION
<u>Reboxetine</u>	Treatment of clinical depression.
<u>Timolol</u>	A non-selective beta adrenergic blocker used in the treatment of elevated intraocular pressure in ocular hypertension or open angle glaucoma.
<u>Efavirenz</u>	A non-nucleoside reverse transcriptase inhibitor used to treat HIV infection or prevent the spread of HIV.
<u>Aprepitant</u>	A substance P/neurokinin 1 receptor antagonist used to treat nausea and vomiting caused by chemotherapy and surgery.
<u>Moricizine</u>	An antiarrhythmic used to treat arrhythmias.
<u>Phenmetrazine</u>	Used as an anorectic in the treatment of obesity.
<u>Ifosfamide</u>	An alkylating and immunosuppressive agent used in chemotherapy for the treatment of cancers, including testicular cancer, ovarian cancer, cervical cancer, osteocarcinoma, bladder cancer, small cell lung cancer, and non-Hodgkin's lymphoma.
<u>Dextromoramide</u>	An opioid analgesic structurally related to methadone and used in the treatment of severe pain. (From Martindale, The Extra Pharmacopoeia, 30th ed., p1070)
<u>Phendimetrazine</u>	A sympathomimetic amine used as adjunct therapy for the short term management of <u>exogeno</u>

DRUG	TARGET	TYPE
<u>Reboxetine</u>	Sodium-dependent noradrenaline transporter	target
<u>Reboxetine</u>	Cytochrome P450 3A4	enzyme
<u>Reboxetine</u>	Cytochrome P450 2D6	enzyme
<u>Reboxetine</u>	P-glycoprotein 1	transporter
<u>Timolol</u>	<u>Beta-1 adrenergic receptor</u>	target
<u>Timolol</u>	Beta-2 adrenergic receptor	target
<u>Timolol</u>	Cytochrome P450 2D6	enzyme
<u>Timolol</u>	P-glycoprotein 1	transporter
<u>Timolol</u>	Cytochrome P450 2C19	enzyme
<u>Timolol</u>		

2. Results and discussion

An over review of the literature concerning the title of this study, it was clear that there is much limited resources for the applications of pyranooxazine compounds may be due to difficult in functionalize the pyrano ring due to the self-condensation of malonyl chloride in producing the pyronic acid so the oxazine ring moiety can be changed by functionalization which is also limited because there is just two ways for getting ne functional group either by the addition to the C=N of the oxazine or substitution of the oxygen moiety but in our patent we introduce new functional group by the addition to the C=N group giving new oxazine having anti-cancer therapeutic applications. We introduce this compound for drug companies and researchers aiming to find its application as a drug. The national cancer institute (NCI) report has revealed that this compound has no toxic effect among the other oxazines from anthranalic acid precursors we found many but not too much pharmaceutical application concerning this type of compound. The most oxazine compounds that achieves pharmaceutical applications were from phenolic precursors for both oxazine and poly oxazine origin and it was clear from the above study that the poly 2-oxazine have attracts the attention of many researchers in studying the efficiency of this polymer which is (water soluble polymer) as drug carrier and self-assembly

polymer for various biomedical application. In this study we have extending our previous review covering the most important oxazine precursors and investigating the pharmaceutical properties associated with these types of compound aiming to develop other methods of action by employing the lab results of these compounds into drug programs then as drug.

3. Conclusion

A review has been done focusing on the oxazine compounds which were derived from Pyronic, Salicylic, Anthranilic acids and Phenols. The review was concentrated on the Synthesis and pharmaceutical applications of these compounds as well as the industrial dyes and polymers derived from oxazine compounds and their significant characteristics as a drugs.

Acknowledgments

I would like to thank the University of Mosul/ College of Science/ Chemistry department for all their cooperation to do this work.

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