

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

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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

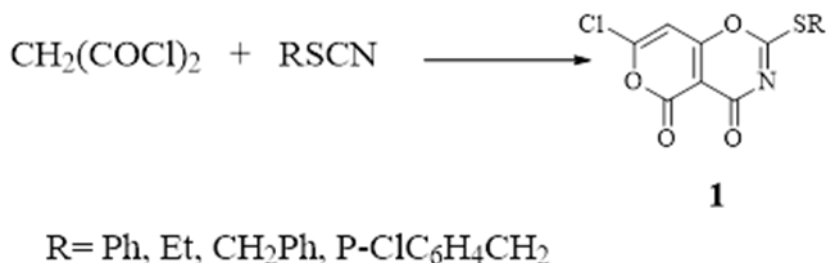
Graphical abstract



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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:

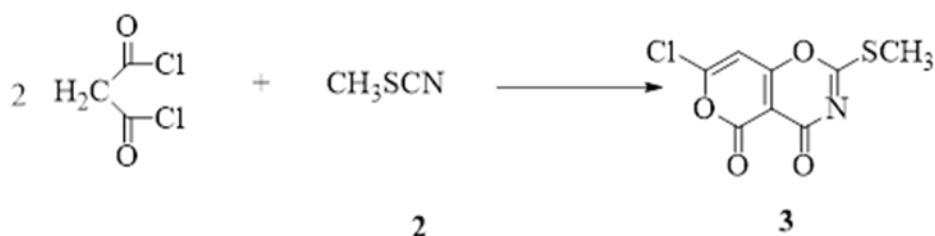


Scheme 1 Pyrano oxazine formation

Some of the synthesized compounds have shown anti-microbial activity against gm +ve and gm -ve 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.

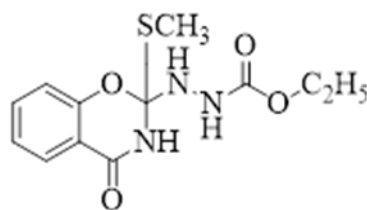


Figure 1 ethyl 2-((2-((methylthio)methyl)-4-oxo-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-yl)hydrazine-1-carboxylate

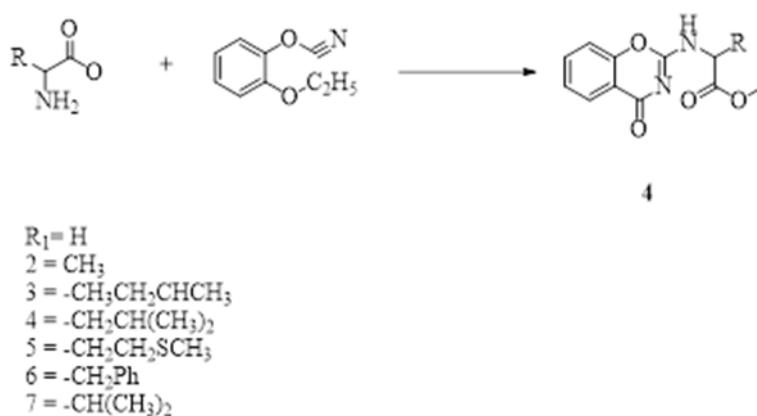
In 2007, Al-ajely and basher have synthesized some 1,3-oxazine from malonyl chloride from methyl and benzyle thiocyanate and reacted the resulted product with some amino acid esters and their hydrazides [20].

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

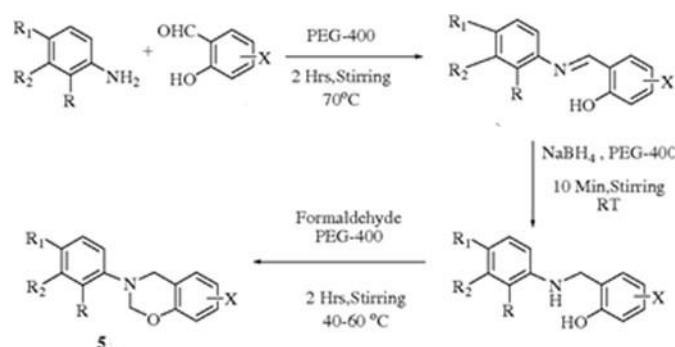
Zilong Tang and his co-workers have prepared N-alkyl-2-aryl benzooxazine from the reaction of benaldehyde with alkyl amines then the formed shiff bases were reduced by sodium borohydride into the corresponding amine then cyclized this amine using TMSCl as catalyst in to the 1,3-oxazine compound. These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



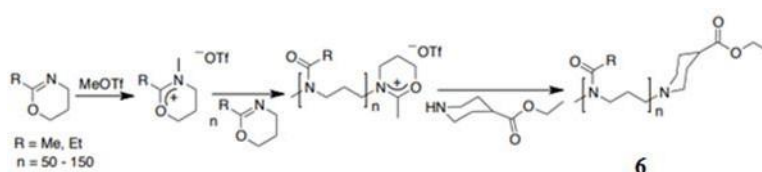
Scheme 3 Synthesis of oxazine derivatives

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].



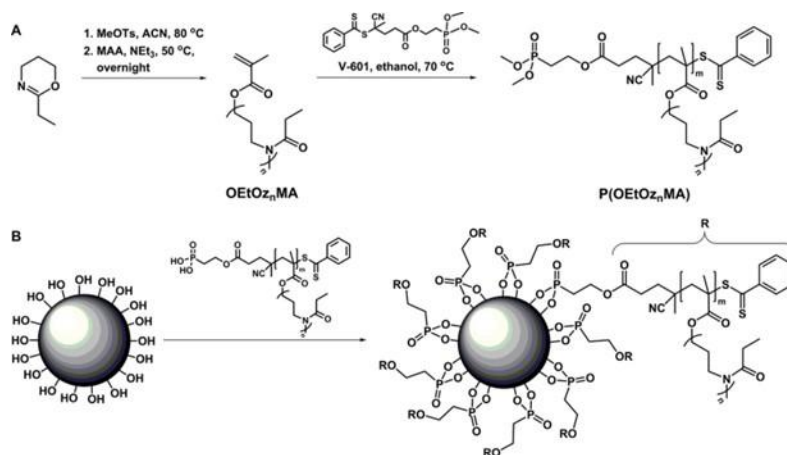
Scheme 4 Formation of dihydro-2H-benzo[1,3]oxazine

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

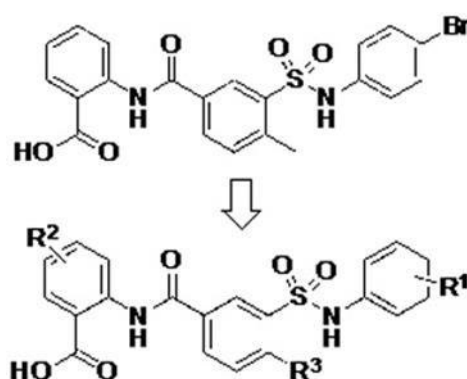


Figure 2 4-Bromo-2-(3-(N-(3,4-dichlorophenyl) sulfamoyl)-4-methyl benzamido) benzoic acid

Guhufran in her thesis has prepared some aroyloxy 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 cromen derivatives with 7-hydroxy-4-methyl-2-thiocoumarin. They found that these compounds were active against in both in vevo and in vitro anti-bacterial effect [79]. Benzekri et-al. Have developed new catalyst for the cyclization of phenols in vevo 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].

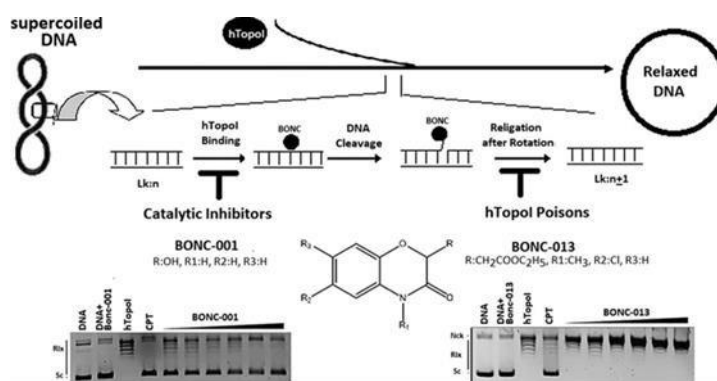


Figure 3 Shows the action of oxazine compound toward the DNA preparing strands.

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].

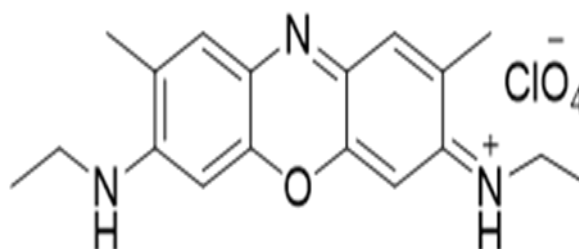
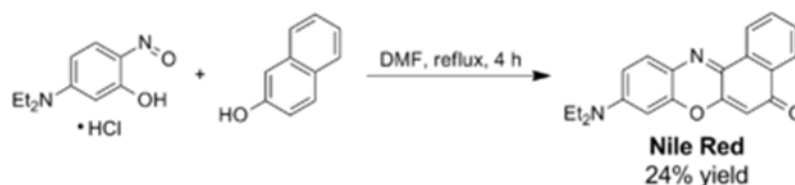


Figure 4 Nile blue dye

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:

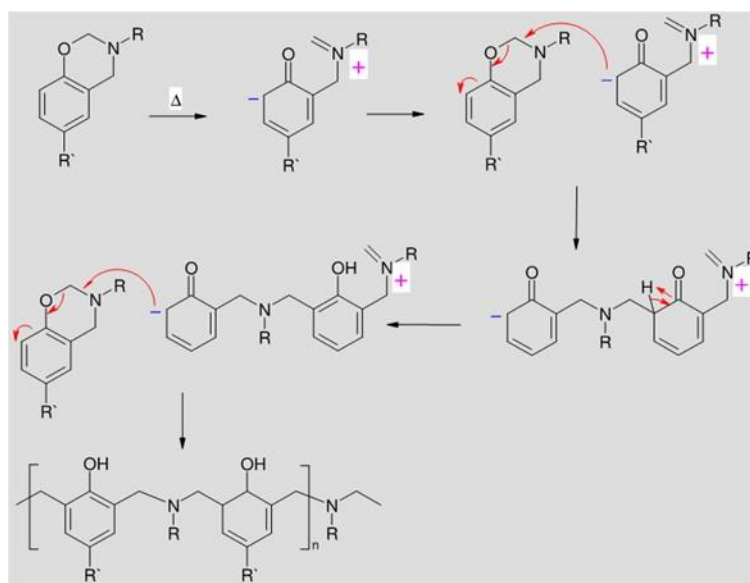


Scheme 8 The synthesis of nile red from β -naphthol

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 bellow 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 reviled 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.

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References

- [1] Davis J, Elvidge JA. Hetrocyclic synthesis with malonyle chloride, J. Chem. Soc. 1952; 4109.
- [2] Elvidge JA, Davis SJ. Hetrocyclic synthesis with malonyle chloride., J. Chem. Soc. 1962; 2606.
- [3] Davis J, Elvidge. Hetrocyclic synthesis with malonyle chloride., J. Chem. Soc. 1962; 3553.
- [4] Davis J, Elvidge A, Foster AB. Hetrocyclic synthesis with malonyle chloride., J. Chem. Soc. 1962; 3638.
- [5] Al Rawi JMA, Elvidge. Hetrocyclic synthesis with malonyle chloride., J. Chem Soc., PerkinTransction, part. 1977; 12(1): 2536.
- [6] Mohammad salman Al-Ajely, Jasim Al-Rawi, John A Elvidge. Heterocyclicsyntheses with malonyl dichloride. Part 13. 6-Chloro-4-hydroxy-2-oxopyran-3-carboxanilides from N-sulphinylanilines and further reactions of malonyl dichloride with thiocyanates J. Chem Soc. Perkin Trans1. 1982; 1577-1178.
- [7] Jasim MA, Al-Rawi, John A Elvidge. Heterocyclic syntheses with malonyl chloride. Part X. 2-Aryl- and -alkyl-thio-7-chloropyrano[3,4-e][1,3]oxazine-4,5-diones from thiocyanates, and their behaviour with amines. Journal of the Chemical Society, Perkin Transactions. 1973; 1.
- [8] Jasim MA, Al-Rawi, John A Elvidge. Heterocyclic syntheses with malonyl chloride. Part XI. Reactions of 2-alkyl-(or -aryl-)thio-7-chloropyrano[3,4-e][1,3]oxazine-4,5-diones with water and with alcohols. Journal of the Chemical Society, Perkin Transactions. 1976; 1(23).
- [9] Jasim MA, Al-Rawi, John A Elvidge. Heterocyclic syntheses with malonyl chloride. Part 12. Confirmatory and revisionary evidence for structures of products derived from 2-alkyl-(or -aryl-)thio-7-chloropyrano[3,4-e][1,3]oxazine-4,5-diones. Journal of the Chemical Society, Perkin Transactions. 1977; 1(23).
- [10] Jasim MA, Al-Rawi, Abdul-Hakim Th. Mahmood. Carbon-13 NMR Spectra of Some 6-Chloro-4-Hydroxy-2-Oxopyrano-3-Carboxyl Derivative, 7-Chloro-Pyrano-1, 3-Oxazine and their Morpholine Reaction Products. An International Journal for Rapid Communication. 1989; 22(10).
- [11] J.M. AL-Rawi, M.S. AL-Ajely and K.D. Sulaiman. Synthesis and antibacterial evaluation of Some Pyrano-1,3--Oxazine Derivatives J. Educ. Sci. 1989, 7, 99.
- [12] J.M.A. AL-Rawi and M.S. AL-Ajely. Synthesis of some substituted pyrano1,3 oxazine. J. Educ. Sci. 1998, , 10, 39..
- [13] H. AL-Mosawi, J.M.A. AL-Rawi and M.S. AL-Ajely. Three-component reaction between kojic acid and aroyl chlorides with ammonium thiocyanate: synthesis of 2-aryl-6-hydroxymethyl-4-thioxo-4Hpyrano[2,3-e][1,3]oxazin-8-ones Arab Gulf. Sci. Res. 1991. 9, 1.
- [14] SM Kupehan, Y Komoda, WA Court, GJ Thomas, KM Smith, A Karim, CS Gilmore, RC Haltivanger, KF Bryan. J. Am. Chem. Soc. 1972; 94: 1354.

- [15] S.M. Kupehan, Y. Komoda, G.J. Thomas and H.P.J. Himtz. Synthesis of 4-aryl-7-methyl-3,4-dihydropyrano [3,4-e] [1,3]oxazine-2,5-dione in aqueous media *J. Chem. Soc. Chem. Commun.* 1972, 1065
- [16] UM Theotino, L Polo Friz, A Gandinin, D Bella. *J. Med. Chem.* 1963; 6: 248.
- [17] Basher HA. Heterocyclic compound synthesis from reaction of Malonyl Chloride and some amino acid Derivatives with their biological study. Ph. D thesis. Mosul university. Mosul. Iraq. 2000.
- [18] Al-Ajely MS, Basher HA. Synthesis of Some Substituted Pyrano 1, 3-oxazine. *National Journal of Chemistry.* 2007; 703-28, 695.
- [19] Al-Ajely MS, Al-Abachi FT. Iraqi patent No. 2000; 287.
- [20] Al-Ajely MS, Basher HA. Synthesis of some substituted pyrano 1,3-oxazine. *National journal of chemistry.* 2007; 28: 695-703.
- [21] Al-Ajely MS, Basher HA. Synthesis and antibacterial evaluation of Some Pyrano-1,3-- Oxazine Derivatives. *National journal of chemistry.* 2007; 26: 348-356.
- [22] Zilong Tang, Zhonghua Zhu, Zanwen Xia. Synthesis and Fungicidal Activity of Novel 2,3-Disubstituted-1,3-benzoxazines. *Molecules.* 2012; 17: 8174-8185.
- [23] Al-Ajely M. Synthesis and Atiplatelet of 2-(ethyl amino acid esters), Amino pyridyl. *Journal of Advances in Chemistry.* 2013; 2(2): 92-97.
- [24] Tyson Belz, Saleh Ihmaid, Jasim Al-Rawi, Steve Petrovski. Synthesis Characterization and Antibacterial, Antifungal Activity of N-(Benzyl Carbamoyl or Carbamothioyl)-2-hydroxy Substituted Benzamide and 2-Benzyl Amino-Substituted Benzoxazines. *International Journal of Medicinal Chemistry.* 2013; 1-20.
- [25] Rahul D Kamble, Shrikant V Hese, Rohan J Meshram, Jivan R Kote, Rajesh N Gacche, Bhaskar S Dawane. Green synthesis and in silico investigation of dihydro-2H-benzo[1,3]oxazine derivatives as inhibitors of Mycobacterium tuberculosis, *Medicinal Chemistry Research.* 2014; 24: 1077-1088.
- [26] Zuzana K, Thomas L, Juraj K, Robert L. Cytotoxicity of 2-oxazines and poly(2-oxazine)s in mouse fibroblast, *Chem Rxiv.* 2018.
- [27] Tobias K, Joshua P, Patrick AJM, de Jongh. Functional Brush Poly(2-ethyl-2-oxazine)s: Synthesis by CROP and RAFT, Thermoresponsiveness and Grafting onto Iron Oxide Nanoparticles., *Macromolecular Rapid communication.* 2019; 40(10).
- [28] Arora RC, Rastogi VK, Agrawal AK, Parmar SS. Synthesis of substituted 2-ethyl-3-(4-hydrazinocarbonylphenyl)-4-quinazolinones and 2-ethyl-3-(4-hydrazinocarbonylmethylphenyl)-4-quinazolinones. *J. Heterocyclic Chem.* 1978; 15: 869.
- [29] Bahadur S, Srivastava N, Mukherji S. Synthesis and antimicrobial evaluation of some new n-substituted benzylidene-6,8-substituted-2-ethyl-quinazolin-4-oxyacetic acid hydrazides. *curr. Sci.* 1983; 52: 910.
- [30] Krantz, A. and Young, J.M., *U.S. Patent* 4873232. *Chem. Abstr.*, Chemistry of 4H-3,1-Benzoxazin-4-ones. 1989; 112, 157888.
- [31] Essawy, A.; El-Hashash, M.A.; EL-Gendy, A.M. and Hamed, M. Compounds derived from acetic acids., *Indian J. Chem.*, 1982. 21B 593.
- [32] Srivastava R. structure studies of a new antitumor agent: tiazofurin and its inactive analogs *J. Indian Chem. Soc.* 1983; 60: 610.
- [33] Mayer JP, Lewis GS, Curtis MJ, Zhang. Solid phase synthesis of quinazolinones., *Tetrahedron Lett.* 1997; 38: 8445-8448.
- [34] Bain, D.I. and Smalley, R.K. *J. Chem. Soc.*, Nitro-substituted 2-phenyl- and 2-(2-tosylaminophenyl)-4H-3,1-benzoxazin-4-ones 1968, 1593.
- [35] Doyle WC, Jr, US Patent. 1972; 3: 970, 652.
- [36] Gilmore JL, Hays SJ, Caprathe BW, Lee C, Emmerling MR, Michael W, Jean C. *Bioorg. Med. Chem. Letters.* 1996; 6: 679.
- [37] Kerdawy MMEI, Yousif MY, Emam AAEL, Moustafa MA, El-Sherbeny MA. Synthesis of new xanthenone derivatives of expected antitubercular activity. *Egypt. J. Pharm. Sci.* 1994; 35(1-6): 1.

- [38] Istvan, H.; Ildiko, S.; Laszol, C.; Jozse, K. and Gyorgy, S. *J. Heterocyclic Chem.*, Synthesis, oxidation and dehydrogenation of cyclic *N,O*- and *N,S*-acetals. Part III. Transformation of *N,O*-acetals: 3-acyl-1,3,4-oxadiazolines. 1993, 30, 1413.
- [39] Peet, N.P. *J. Heterocyclic Chem.*, On Triazoles. The acylation of 5-amino-1,2,4-triazoles. 1987, 24, 223.
- [40] Saillaja S, Rao E, Rajanarender TE, Krishnamurthy AA. Synthesis of 3-(5-methyl-3-isoxazolyl)-2-styrylquinazolin-4(3*H*)-ones and their antifungal activity. *J. Indian Chem. Soc.* 1988; 65: 200.
- [41] Clemence, F.; Le Martret, O.; Delevallee, F.; Benzoni, J.; Jouquey, S.; Mouren, M. and Deraedt, R. 4-Hydroxy-3-quinolinecarboxamides with antiarthritic and analgesic activities. *Med. Chem.*, 1988, 31, 1453.
- [42] Clemence F, Le Martret O, Delevallee F. U.S. Patent. 1985; 4: 636, 512.
- [43] Marsham, P.R.; Jackman, A.L.; Barker, A.J.; Boyle, F.T.; Pegg, S.J.; Wardleworth, J.M.; Kimbell, R.; O'Connor, B.M.; Calvert, A.H. and Hughes, L.R. Quinazoline Antifolate Thymidylate Synthase Inhibitors: Replacement of Glutamic Acid in the C2-Methyl Series. *J. Med. Chem.*, 1995, 38, 994.
- [44] Amin MA, Osman AN, Aziza MA, El-Hakim AE. Synthesis and reaction of 2-chloromethyl-3,1-benzoxazin 4-ones with amines. *Egypt. J. Chem.* 1995; 38(1): 113.
- [45] Medstrom, L.; Moorman, A.R., Dobbs, J. and Abeles, R.H., Inhibition of serine proteases by peptidyl fluoromethyl ketones. *Biochemistry*, 1984 23, 1753.
- [46] Doyle WC, Jr, US Patent. 1972; 3: 970, 652.
- [47] Shrimai, M.; Kalsi, R.; Dixit, K.S. and Barthwal, J.P. Application of sulfonic acid functionalized nanoporous silica (SBA-Pr-SO₃H) in the green one-pot synthesis of triazoloquinazolinones and benzimidazoquinazolinones, *Arzneim Forsch*, 1991. 41 (5), 514.
- [48] KulKarni, Y.D.; Bishnoi, A. and Dua, P.R. Chemistry of 4*H*-3,1-Benzoxazin-4-ones. *J. Indian Chem. Soc.*, 1990, 67, 852.
- [49] Schmidt, R.R. and Schneider, R. Acyclic Stereoselective Synthesis of Carbohydrates. *Tetrahedron Letters*, 1970, 5095.
- [50] Fenton, G.; Newton, C.G.; Wyman, B.M.; Bagge, P.; Dron, D.I.; Riddell, D. and Jones, G.D. Hypolipidemic 2-[4-(1,1-dimethylethyl)phenyl]-4*H*-3,1-benzoxazin-4-ones. Structure-activity relationships of a novel series of high-density lipoprotein elevators. *J. Med. Chem.*, 1989, 32, 265.
- [51] Catarzi, D.; Cecchi, L.; Colotta, V.; Filacchioni, G.; Martini, C.; Tacchi, P. and Lucacchini, Synthesis and Structure-Activity Relationships of a New Set of 2-Arylpyrazolo[3,4-*c*]quinoline Derivatives as Adenosine Receptor Antagonists. *A. J. Med. Chem.*, 1995, 38, 1330.
- [52] Ashare, R. and Mukerjee, A.K. Chemistry of 4*H*-3,1-benzoxazine-4-ones. *Indian J. Chem. Sect. B*, 1986, 25, 1180.
- [53] Jarvest, R.L.; Parratt, M.J.; Debouck, C.M.; Gorniak, J.G. Jennings, L.J.; Serafinowska, H.T. and Striekler, J.E. Synthesis and antifungal activity of new azole derivatives containing an oxathiane ring *Bioorg. Med. Chem. Lett.*, 1996, 6, 2463.
- [54] Kumar, P.R. and Reddy, M.S. Aromatic ketones containing at least one acetyl group and one other acyl group. *Indian J. Chem., Sect B*, 1991, 30B (3), 366.
- [55] Rabilloud, G. and Sillion, B. phosphono-Substituted Isoindolines and Indoles from 2,3- and 2,4-Benzoxazin-1-ones *Bull. Soc. Chim. France*, 1975, 2682.
- [56] Auberson, Y.P. and Winkler, T. Cyclization of *N*-acylanthranilic acids with Vilsmeier reagents. Chemical and structural studies. *Synthesis*, 1994, 470.
- [57] Balsubramanian, V. and Argade, N.A. Reactions of an electrophilic glycine cation equivalent with Grignard reagents a simple synthesis of β -X-unsaturated amino acids. *Tetrahedron Lett.*, 1986, 27, 2487.
- [58] Misra, V.S.; Saxena, V.K. and Mohamed, M.M.; El-Hashash, M.A.; El-Gendy, A.M.; Mohamed, I. and Sayed, O.A. Synthesis of Some Novel 3-(4-Pyridinyl)-6-aryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles *J. Chem. Soc. Of Pakistan*, 1986, 8, 3, 371.
- [59] Teshima, T.; Griffir, J.C. and Powers, J.C. NMR Studies of Fluorinated Serine Protease Inhibitors *J. Biol. Chem.*, 1982, 257, 5085.

- [60] Augelli-Szafran, C.E.; Caprathe, B.W.; Gilmore, J.L.; Hays, S.J.; Jean, J.C. and Penvose-Yi, J.R. *U.S. Patent* 5652237, National Historic Chemical Landmark, *Chem. Abstr.* 1997, 127, 176430.
- [61] Hahn E, Glas G, Guenther P. German Patent 4, 101, 380 (1991); *Chem. Abstr.* 1992; 117: 171-462.
- [62] Fujii, K.; Uejima, Y.; Oshida, J.; Kawabata, H.; Kokubo, M.; Sato, O. and Kato, Y. *Japanese Patent* JP 08134050; Chemistry & Biochemistry. *Chem. Abstr.*, 1996, 125, 168648.
- [63] Uejima, Y.; Oshida, J.; Kawabata, H.; Kokubo, M.; Kato, Y. and Fujii, K. Reduction in muscarinic receptors by antisense oligodeoxynucleotide. *Biochem. Pharmacol.*, 1994, 48, 426.
- [64] Vaid, R.K.; Rao, B.; Kaushik, B and Singh, S.P. Total synthesis of crystalline ($\pm$)-fredericamycin A.m, *Indian J. Chem., Sect. B*, 1987, 26, 376.
- [65] Soliman AY, Attia IA, Salem MA, Soliman EA, Gaber AM. *Chin. J. Chem.* 1996; 14(5): 437.
- [66] Walsh, D.A. Antiinflammatory agents. 3. Synthesis and pharmacological evaluation of 2-amino-3-benzoylphenylacetic acid and analogs. *Synthesis*, 1980, 677.
- [67] Mahmoud M, El-Hashash M. *Revue Roumaine de Chimie.* 1979; 24: 849.
- [68] Irani S, Nikpour F. An Efficient Approach for the Synthesis of N-Phenylcarboxamido-2-aryl-1,2-dihydro-(4H)-3,1-benzoxazine-4-ones, *J. Iran. Chem. Soc.* 2010; 7(4): 859-863.
- [69] Anilkumar R. synthesis, characterization and biological activity of 1,3-benzoxazine derivatives. Msc. pharmacy thesis , Rajiv Gandhi University of health science. Karnataka. Bangalore. India. 2011.
- [70] Osman MO Habib, Hussein M. Hassan, Ahmed El-Mekabaty. Studies on Some Benzoxazine-4-one Derivatives with Potential Biological Activity. *American Journal of Organic Chemistry.* 2012; 2(3): 45-51.
- [71] Mohamed A. Abd-Elhakeem, Ahmed M. Elsayed. Synthesis and antimicrobial activity of some new 2,3-disubstituted quinazoline-4(3H)-ones derivatives, *Journal of Chemical and Pharmaceutical Research.* 2013; 5(5): 275-279.
- [72] James D Patrone et-al. Identification and Optimization of Anthranilic Acid -Based Inhibitors of Replication Protein A, *ChemMedChem.* 2016; 11(8): 893-899.
- [73] Ghufraan T Sadeek, Mohammad S. Al-Ajely, Neim H Saleem. New Approach for the Synthesis of Aryloxy 1,3-Oxazines, *Journal of Material Sciences & Manufacturing Research.* 2020; 1(2): 1-5.
- [74] Ghufraan T Sadeek. Synthesis of some heterocyclic compounds(oxazines) and the study of their biological activities ,PhD. Thesis, Mosul university Mosul-Iraq. 2021.
- [75] Chylinska JB, Urbanski T. Dihydro 1,3-oxazine derivatives and their antitumor activity. *Journal of Medicinal Chemistry.* 1962; 6: 484.
- [76] Zuhal T, Emel P, Adem K. Synthesis of New 1,3-Disubstituted-2,3-dihydro-1H-naphth-[1,2e][1,3]oxazines. *Molecules.* 2010; 12: 345-352.
- [77] Ramian M, Shanmugam M. Synthesis and biological activity of 6-alkyl/chloro-3-{4-(6- alkyl/chloro-2H -benzo [e] [1,3-oxazine-3-(4H)yl} phenyl-3,4-dihydro-2H benzo [e] [1,3] oxazine. *Indian journal of chemistry.* 2010; 49B: 1083-1087.
- [78] Zhang RR, Liu. J. Microwave-assisted synthesis and antifungal activity of novel coumarin derivatives: Pyrano[3,2-c]chromene-2,5-diones. *European Journal of Medicinal Chemistry.* 2016; 28 Mar: 116: 76-83.
- [79] Bijoy P Mathew, Nisha Aggarwal, Rajesh Kumar, Mahendra Nath. Synthesis and anti-bacterial activity of novel dihydrochromeno [8, 7-e][1, 3] oxazine-2 (8H)-thiones. *Journal of Sulfur Chemistry.* 2014; 35: 31-41.
- [80] Z Benzekri, S Hamia, R Benhdidou, H Serrar, S Boukhris, A Hassikou, A Souizi. One-pot solvent-free synthesis of naphtho[1,2-e][1,3]oxazin-3-one/thione derivatives using a snail shell as a green and efficient catalyst. *Journal of Materials and Environmental Sciences.* 2017; 8(8): 2986-2992.
- [81] Pradeep K, Jaiswal V, Sharma J, Prikhodko I. On water ultrasound-assisted one pot efficient synthesis of functionalized 2-oxo-benzo[1,4]oxazines: First application to the synthesis of anticancer indole alkaloid, Cephalandole A. *Tetrahedron Lett.* 2017; 03: 048.
- [82] Dhafer S Zinad, Ahmed Mahal, Ranjan K. Mohapatra, Ashish K Sarangi. Medicinal chemistry of oxazines as promising agents in drug discovery. *Chem Biol Drug Des.* 2019; 00: 1-32.

- [83] Egemen Foto, Çigdem Özen. Benzoxazines as new human topoisomerase I inhibitors and potential poisons. DARU Journal of Pharmaceutical SciencesDARU. Journal of pharmaceutical science. 2019; 28: 65-73.
- [84] Ondrej S, Richard H. Drug delivery systems based on poly(2-oxazoline)s and p(2-oxazine)s. ADVANCED THERAPEUTICS. 2020; 3(1).
- [85] Margaret R, Lewis Phillp pG, Henry A. The Action of Oxazine Dyes on Tumors in Mice'. Cancer Research. P. 2021; 736.
- [86] <https://en.wikipedia.org/wiki/Oxazines>.
- [87] Ewa M. Czekanska. Assessment of cell proliferation with resazurin-based fluorescent dye. Methods in Molecular Biology book series. 2011.
- [88] David S. Wishart .a major update to the DrugBank database for 2018. *Nucleic Acids Research*, 2018, Vol. 46, Database issue.
- [89] Jiney Jose, Aurore Loudet, Yuichiro Ueno, Rola Barhoumi, Robert C Burghardt, Kevin Burgess. Intracellular imaging of organelles with new water-soluble benzophenoxazine dyes. *Org Biomol Chem*. 2010; 8(9): 2052-9.
- [90] JL Vennerstrom, MT Makler, CK Angerhofer, JA Williams. Antimalarial dyes revisited: xanthenes, azines, oxazines, and thiazines. *Antimicrob agents chemother*. 1995; 39(12): 2671-7.
- [91] Harith M. Al-Ajely. The synthesis and pharmaceutical profile of chalcones and their oxazine compounds. *Acta Scientific pharmacology*. 2021; 2(4).
- [92] Vijayakumara CT, Shamim Rishwanab S, Surendera N. Structurally diverse benzoxazines: synthesis, polymerization, and thermal stability, *Designed Monomers and Polymers*. 2014; 17(1): 47–57.
- [93] Amal F Jaffar. The effect of polymer blend on the third order nonlinearity of oxazine dye doped films by using z-scan techniques. *Journal of Al-Nahrain University*. 2015; 18(3): 80-88.
- [94] Palanikumar L, Sum. aya Al-Hosani. pH-responsive high stability polymeric nanoparticles for targeted delivery of anticancer therapeutics communications biology. 2020; 3: 95.
- [95] Richard Hoogenboom. Drug Delivery Systems Based on Poly(2-Oxazoline)s and Poly(2-Oxazine)s, *Advanced Therapeutics*. 2019; 201900168.
- [96] Zivani Varanaraj, Jungyeon, Kim C. Remzi Becer. Poly(2-oxazine)s: A comprehensive overview of the polymer structures, physical properties and applications. *European Polymer Journal*. 2021; 47: 110299.
- [97] Young-Jin Kimab, Yukiko T Matsunaga. Thermo-responsive polymers and their application as smart biomaterials, *Journal of Materials Chemistry B*. 2017; 23.
- [98] Anna Z, Robert L. Poly(2-oxazoline)- and Poly(2-oxazine)-Based Self-Assemblies, Polyplexes, and Drug Nanoformulations-An Update. 2021.
- [99] Zivani Varanaraj, Jungyeon Kim C, Remzi Becer. Poly(2-xazine)s: A comprehensive overview of the polymer structures, physical properties and applications, *European Polymer Journal*. P. 2021; 110299.
- [100] Anna Z, Robert L. Poly(2-oxazoline)- and Poly(2-oxazine)-Based Self-Assemblies, Polyplexes, and Drug Nanoformulations-An Update. *Adv. Healthcare Mater*. 2021; 2001382: 1-27.
- [101] Ondrej S, Kathleen L, Bart V. Unexpected Reactivity Switch in the Statistical Copolymerization of 2-Oxazolines and 2-Oxazines Enabling the One-Step Synthesis of Amphiphilic Gradient Copolymers, *J. Am. Chem. Soc*. 2019; 141(24): 9617-9622
- [102] Jonathan B Grimm, Brian P English. A general method to improve fluorophores for live-cell and single-molecule microscopy. *Naturemethods*. 2015; 12: 244–250.