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Research Article

Synthesis of Some New Oxazine Compounds Derived from Phenols and Schiff Bases

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Abstract

The implication of heterocyclic compounds in most of the drugs used in the market and the timely need for changing drugs due to the drug resistance encourage researchers to synthesize new heterocyclic compounds especially those with oxygen and nitrogen heteroatoms which according to recent FDA reports. They form of 90 percent as anti-tumor agent and about 75 percent of the other diseases. Accordingly in the present research new oxazine compounds have been synthesized from two routes. The first one by grinding technique using formaldehyde, aromatic amines and methanolic ammonia to the synthesis of compounds (A1-5) as a one pot three components reaction system. The second route including the condensation of some aryl aldehydes with antharanilic acid (A6) then the resulting Schiff bases (A7-11) were cyclized using acetic anhydride into the corresponding oxazine compounds (A12-16) This type of reaction including the loss of a molecule of acetic acid molecules from (the solvent)anhydride. The anhydride containing the evolved acetic acid was used several times for some more reaction samples keeping its efficiency during the cyclization process. All the synthesized oxazines were studied using IR,[1] HNMR methods and are discussed.

Keywords: Synthesis; Oxazine Compounds; Phenols and Schiff Bases

Introduction

As it was mentioned above concerning the importance of hetero cyclic compounds as drug or co-drug compounds. Researchers always provides the market with new drug discovery research leading into new drug product. Oxazine compounds have proved to be used as drug according the works of many researchers. The synthesis of this type of heterocyclic compounds were achieved from different precursors, Either from antharanilic acid and its derivatives by ring closure either by acetic anhydride [1,2] or by chloro acetyl chloride [3] or succinic anhydride [3] or by alkyl chloro acetate [4] and ethyl ester derivatives [5] for example cyano ethyl ester. There were another methods for the synthesizing of oxazine compounds from other than antharanilic acid [6-11] among these precursors are the amido salicylate [12,13] cyclized by different reagents [14-17] some were cyclized using Vilsmeier-Haack reaction. The cyanate derivative were also cyclized into oxazine [18-21]. It was reported in the literature that cyanate derivatives of antharanilic acid when allowed to react with amino acid esters afforded the quinazoline derivatives and these compounds showed a biological effects in which the water solution of these compounds had HLE and human sputum elastase activities [22,23]. The above work encourage many researchers to develop new synthetic pathways in synthesizing this type of heterocyclic compounds. So Anilkumar. R. has published the synthesis of some oxazine compounds from antharanilic acid. These compounds have showed anti-inflammatory activities [24]. Osman and his co-workers have synthesized oxazine compounds from antharanilic acid containing sulfonic ester moiety, These compounds have been tested against *Bacillus Thuringenesis* and *Klebseilla Pneumonia* and showed remarkable activity against these micro organisms [25]. James D. Patronea and his co-workers

have prepared 4-Bromo-2-(3-(N-(3,4-dichlorophenyl) sulfamoyl)-4-methyl benzamido) benzoic which is a derivative of antharanilic acid. This compound was found to be active toward inhibition the Replication of Protein A (RPA) which is specific in distribution of proten-proten interaction that make them as therapeutic cancer target [26]. Guhufran has synthesized aroyloxy oxazines from antharanilic acid. She tested these compounds against Gram +ve and Gram -ve bacteria and got excellent screening effects [27,28]. Among the studied oxazines derived from phenols are the work of Zuhal et-al. whom they prepared oxazines and studied their medical applications [29]. In 2014 Mathew and co-workers have prepared cromino oxazine from hydroxyl cromine and 7-hydroxy 4-methyl-2- thio coumarin and screening these compounds against some micro organism *in vivo* and *in vitro* studies [30]. Fadia and here co -workers have synthesized some coumarin compounds from resorcinol and ethyl aceto acetate using pole styrene sulfonic acidAmberlyst-15) as catalyst via Pechmann condensations [31]. Monar and co-workers have synthesized some coumarin derivatives and studied Antioxidant Activity Using ABTS Inhibition, their protective activity against DNA damage induced by the bleomycin-iron complex [32].

Pradeep K., *et al.* have synthesized some 1,3-oxazine compounds, These compounds were used in the synthesis of Cephalandole A an anti -cancer indole type compounds with 80% yield [33]. Dhafer., *et al.* recently have published a review on the synthesis and biological applications of oxazine compounds [34]. Çigdem Özen and co-workers have studied the action of some 1,4-oxazines as DNA strand repairing agent [35]. 84. S. Ondrej and H. Richard have studied poly(oxazine)s of phenolic precursors and the found that this polymer can be used as drug carrier an alternative PEG and poly (N-hydroxypropylmethacrylamide) usually used in the market nowadays [36] in our study we used two different methodologies in the synthesis of oxazine compounds aiming to study there biological effects in our drug discovery program.

Experimental

All melting points were uncorrected using electro thermal type SMP30 UK melting point apparatus. IR spectra were measured using Alpha (ATR) instrument. ^{1}HNMR spectra were recorded using Varian Agilent Type 499.53MHZ, DMSO as internal solvent. All chemical were supplied by Sigma- Aldrich and Fluka chemical companies. 7-hydroxy-4-methylcoumarin-8-carbaldehyde was prepared according to the well-known procedure [37]. 2-Chloro-3-formyl quinolone was also prepared according to the well-established procedure [38].

Synthesis of oxazine compounds(A1-5)

General procedure

Following the same published procedure [39] Formaldehyd (0.2 ml), $ZrOCl_2$. $8H_2O$, (0.2 mol., 5.8g), Aromatic amine (0.1mol) and Euginol or 1-Naphtol (0.1 mol) were mixed together in ceramic mortar and pistil. The mixture were grinded for30 minutes, dichloromethane about 25 mil. was then added. The organic layer was then separated, washed with brine then with water twice and dried over $MgSO_4$ anhydrous. Evaporation of the solvent affords the crude products of the titled compounds. Crystallization from ethanol gave pure product. The physical properties were listed in Table1.

Table 1: Physical properties of compounds(A1-5).

Synthesis of 2-carboxy aryldine aniline(A7-11)

General procedure:

These compounds were synthesized following an elsewhere published procedure [40] with some modification on the method. So Aromatic aldehyde (0.01 mol.), antharanilic acid (0.01 mol.) were mixed together after that methanol (15 ml.) was then added and two drops of glacial acetic acid. The final mixture was refluxed for one hour. And monitored by TLC, solvent was evaporated under reduced pressure. The resulted final product was recrystallized. The physical properties were shown in Table2.

Synthesis of compounds (A12-16)

The products of the previous method was dissolved in acetic anhydride, then it was refluxed for 3hours. The solvent was removed

under reduced pressure and re used again for the rest of compounds. The final product was recrystallized from methanol. The physical properties of the final compounds were shown in Table 3.

Table 2: Physical properties of compounds(A7-11).

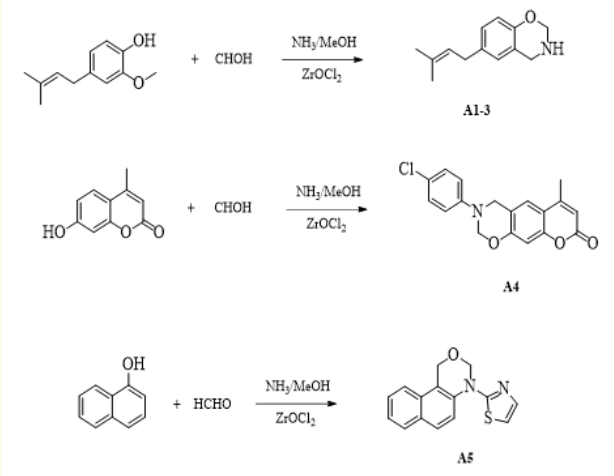
Table 3: Physical properties of compounds(A12-16).

Results and Discussion

Using grinding technique compounds (A1-5) were prepared Scheme1 and were characterized by the combination of IR and1H NMR methods as follows:

N-4-Nitro phenyl-6- [(1-propenyl)-7-methoxy] [3,-e] benzoxazine A1

IR cm-1: 1600,1529 for C=C Aromatic, 1262, 1142 C-O-C, 1498, 1230 for asym and sym. stretch for NO2, ^{1}HNMR(ppm); 3.3(d,2H) for eugenol aliphatic protons, 4.7,5 (d,t2H) alkene protons, 3.78 (s,3H) OCH3, 4.9, 6(d of d 4H) AB aromatic., 6.79(s,2H) aromatic, 8.02-8.1(d,2H) AB pro tons near NO2 group.



Scheme 1

N-2-Nitrophenyl-6- [(1-prppylenyl)-7 methoxy [3,1-e] benzoxazine A2

IR cm^{-1}: 1611,1590,1505 for C=C Aromatic,1136, 1197 f or C-O-C, 1440, 1277 for aSym and sym. stretch forNO_2, ^{1}HNMR(ppm); 3.3(d,2H) of eugenol,3.7(s,3H) of OCH_3, 4.6(s,2H) for CH2N of Oxazine 4.7(2H) of CH_2 euginol, 6.7(s,2H) for OCH2N of oxazine, 7.1-7.7(m,4H), 7.73(s,d2H) aromatic protons and ortho protons to the NO_2 group respectively.

N-2-Bromophenyl-6- [91-propenyl-7-mothoxy] [3,1-e]benzoxazine A3

IR cm^{-1}: 3011 for C-H, 1617 for C=C, 16051 C=C, 1507 for C=C Aromatic, ^{1}HNMR(ppm); 3.32 (d,2H) CH_2 of eugenol aliphatic protons, 3.3 (s,3H) OCH_3, 4.9(t,1H) olefinic proton, 4.7 5and5 (t,2H) for olefinic CH2 protons.

N-4-Chlorophenyl-6-(3-methyl) [3,1-e] Cumarinyl oxazine A4

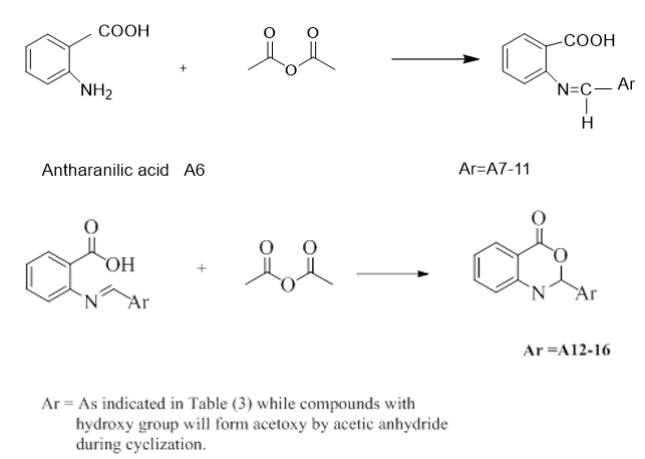
IR cm^{-1}:3080 forC-H,1792 for C=O lactone, 1662 for C=C, 1596, 1541 for C=C Aromatic, 1451, 1260 for asym and sym. NO_2, 1388, 1260 for C-O-C, 1213 for C-N, ^{1}HNMR(ppm); 2.3 (s,3H) CH3, 2.6(s,2H) C_5 of coumarin ring, 4.8(s,2H) C4 oxazine ring, 6.13(s,2H)

C_2 oxazine, 7.13,7.12 (d,2H) A protons Of AB system, 6.8, 7.0(d,2H) of B type protons.

N—Thiazolyl [3,1-e [naphthaoxazine] A5

IR cm^{-1}: 3022 for C-H, 1647, 1635 for C=N, 1596, 1577 for C=C aromatic,1318 for C-N, 752 for C-S, ^{1}HNMR(ppm); 3.35(s,2H) – CH_2N, 4.92(s,2H) for- OCH2, 6.5, 6.8(d,2H) thiazole, 6.88-7-8(m,6H) aromatic.

Schiff bases compoundsA7-11, Scheme 2. were characterized by the mainIR absorption peaks at1605$cm^{-1}$for aromatic, C=C aromatic and at 1330 cm^{-1} for C-O.



Scheme 2

Compounds A 12-16 as shown above in scheme2.were characterized as follows :

N-Acetyl-2-(2-methoxy phenyl) [3,1-e] benzoxazine-4-one A12

IR cm^{-1}: 1771, C=O lactone 1684 for C=O Amide, 1646 for C=O amide, 1600, 1541 for C=C Aromatic,776 for C-Cl, ^{1}HNMR(ppm); 2.1 (s,3H) for CH3CO, 2.3(s,3H) for CH_3COO, 3.8(s,3H) for OCH_3, 6.9, 7.13, 7.4(d and singlet) 3H of vanilin residue protons, 7.6,7.9 and 7.99(m,4H) aromatic protons of benzoxazine ring.

N-Acetyl-2-(methoxy phenyl-2-yl) [3,1]benzoxazine -4-oneA13

IR cm^{-1}: 3056 for C-H, 1685 for C=O lactone, 1653 for C=O amide, 1606, 1540 for C=C aromatic, 1143 for C-O,^{1}HNMR(ppm); 2.1(s,3H) for CH_3CON, 2.3(s,3H), 3.17(s,3H) for OCH3, 7.1-7.9(m,7H) aromatic, 8.4 (s,1H) C_2 of oxazine ring proton.

N-acetyl-2- [5-methyl-7-acetoxy cumarin-8-yl] [3,1benzoxazine-2-one A14]

- IR cm^{-1}: 2926 for C-H, 1792for C=O lactone, 1746,1716 for ester, 1696 for C=O amide, 1600, 1540 Aromatic, ^{1}HNMR(ppm);
- 1.9(s,3H) CH3CON, 2.3(s,3H)for - CH_3, 2.4(s,3H) forCH_3 COO, 6.43(d1H) C_3 of coumarin proton, 7.1(d,1H) for C_4, 7.4-8 (m,6H) Aromatic.

N-Acetyl-2-(2-Chloro quinolin-2-yl) [3,1-e] benzoxazine-4-one A15

3056 for C-H, 1733 for ester, 1668 for C=O amide, 1637 for C=N, 1606, 1507 for C=C aromatic, 788 f or C-Cl, ^{1}HNMR(ppm); 2.1(s,3H) for CH3CO, 7.1-8 (m9H) aromatic, 8.47 (s,1H) for C_2 oxazine ring.

N-Acetyl-2-(2-fury) [3,1]benzoxazine-4-one A16

IR cm^{-1}: 2927 for C-H, 1771f or C=O lactone, 1665 for C=O amide, 1490, 1608 for C=C Aromatic, 1339, 1145 for C-O-C, ^{1}HNMR; 2.2(s,3H) CH3CO, 6.6,6.9 (d,2H) furan protons, 7.54(d,1H) furan proton, 7.64-7.9 (m,4H) aromatic, 8.0(s,1H0 for oxazine protons.

It is with to note that this work is extension to our previous work [44-46]. So adding new moiety for oxazine ring which is vanillin and nitrogenous residue will might increase the biological effects. We know that vanillin itself known to have antioxidant properties and oxazines also known to have versatile biological applications so making a combination of both may cause to improve the therapeutic impact of this type of compounds.

Conclusions

In conclusion to the above work it is clear that using one pot three component system and two steps cyclization reaction of antharanilic acid with some aromatic aldehydes resulted into the formation of new oxazine derivatives. The IR and ^{1}HNMR studies of the above studied compounds revealed it formation through their structures confirmations. The other step of study will be their biological study which is our next goal.

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