SYNTHESIS, CHARACTERIZATION AND ANTI-INFLAMMATORY EVALUATION OF SUBSTITUTED QUINAZOLINONE DERIVATIVES

Meenu Chaudhary*1, S. Bhattacharya2, Yusra Ahmad3

*1Division of Pharmaceutical Sciences, S.G.R.R.I.T.S. Patel Nagar, Dehradun, Uttarakhand-248001, India
2Department of pharmaceutical Chemistry, SIP, Allahabad, Uttar Pradesh- 211003, India.
3Department of Pharmacology, Uttrakhand Technical University, Dehradun, Uttarakhand-248001, India.

Corresponding author*: meenu-mpharm_chem@yahoo.co.in

ABSTRACT: Quinazolinone is a compound made up of two fused six member simple aromatic rings-benzene and pyrimidine ring and have been reported to posses versatile type of biological activities such as anticaner, anticonvulsant, anti-inflammatory, anthelminthic, antimicrobial activities. A series of novel substituted-[1,2,4]triazolo[1,5c]quinazolinone derivatives (K11-19) were synthesized by manich reaction using formamide and different secondary amines. Structures of compounds synthesized were confirmed by IR, 1H-NMR and Mass spectroscopic analysis. All synthesized compounds were screened for anti-inflammatory activity. The anti-inflammatory activity was performed at concentration (100 mg/kg body mass) by rat paw oedema model. Diclofenac sodium (50 mg/kg) was used as standard.

All synthesized compounds have shown anti-inflammatory activity as all has significant reduction in inflammation when compared to inflammatory control group. Compounds K 15, K 18 and K 19 have shown very good anti-inflammatory activity comparable to standard drug Diclofenac sodium.

Keyword: [1,2,4]triazolo[1,5c]quinazolinone derivatives; anti-inflammatory activity; manich reaction.

1. Introduction

Quinazolinone is the major fused six-member heterocyclic ring system and is one of the most encountered heterocyclic in medicinal chemistry and a building block for around 120 naturally occurring alkaloids. Quinazolinone constitute an important class of medicinally important small molecules which have been reported to possess anticonvulsant1-3, antimicrobial4-8, anti-inflammatory9-11, antitumor12, anticancer13, sedative-hypnotic14, diuretic15-16, antiviral17, antihypertensive18 activities. Several 2, 3-disubstituted Quinazolinone derivatives were synthesized and tested for different biological activities. These reports showed that aryl substitution at 2nd and 3rd position enhances biological activities.

Efforts towards the development and identification of new molecules for anti-inflammatory activities with minimal gastrointestinal ulceration side effects have gained significance in the recent past during which the quinazolinones came into the scenario. With the revelation of exploring the diverse pharmacological nature of [1,2,4]triazolo[1,5c]quinazolinone derivatives, it was contemplated to synthesize some substituted quinazolinone derivatives by manich reaction having general structure of figure 1 as potential anti-inflammatory agents.

Figure 1

2. Materials and Methods

2.1 Chemistry: Substituted-[1,2,4] Triazolo[1,5c]Quinazolinone derivatives were synthesized by five steps. 2-methyl-benzoaxazin-4-one was prepared by using acetic anhydride. Treating it with semicarbazine to produce corresponding (2-methyl-4-oxo-quinazolin-3-yl)-urea; which further heated above its melting to get 5-methyl-[1,2,4]triazolo[1,5c]quinazolin-2-one respectively. To the stirred solution of an
equivalent amount of 5-methyl-[1,2,4]triazolo[1,5c]quinazolin-2-one and appropriated benzaldehyde in ethanol was added aqueous NaOH solution (10% w/v, 10ml). The title compounds could be obtained by mannich reaction using formamide and different secondary amines. Melting points were recorded in open capillaries with electric melting point apparatus and were uncorrected. IR spectra (KBr disks) were recorded using Shimadzu 8400S FTIR spectrophotometer. 1H-NMR were recorded in Bruker Avance II (400 MHz) spectrophotometer in CDCl3 solution and chemical shift values were reported in ppm relative to TMS (δ = 0) as internal standard. Mass spectra were recorded on a Shimazu LC-MS (2010A) spectrophotometer. TLC was performed on silica gel coated plates for monitoring the reactions.

2.2. Experiment

2.2.1 Preparation of 2-methyl-benzoxazin-4-one: A mixture of (6.8 g, 0.1 mole) anthranilic acid and acetic anhydride (11 ml, 0.02 mole) was refluxed for 6 hours and while hot poured into cold water. Allow the reaction mixture to cool at room temperature then washed with methanol, residue was dried at room temperature further recrystallized with methanol and dried.

2.2.2 Synthesis of (2-Methyl-4-oxo-4H-quinazolin-3-yl)-urea: An equi-molar quantity (8.5 g, 0.05 mole) of 2-methyl-benzoxazin-4-one and semicarbazide were dissolved in ethanol separately. Then, mixture was refluxed for 1 hour with glacial acetic acid. After the completion of reaction, contents were cooled to room temperature. Solid mass was collected and recrystallized with methanol.

2.2.3 Synthesis of 5-methyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one: The product obtained from step 2 was heated above its melting point to get 5-methyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one. Product was recrystallized with methanol.

2.2.4 Synthesis of substituted-[1,2,4]triazolo[1,5-c]quinazolin-2-one: An equimolar mixture (0.01mole) of 5-methyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one and substituted benzaldehyde was fitted with mechanical stirrer, and solution was immersed into cold water bath. To this, 10% of NaOH solution was added slowly until the mixture become just acidic to litmus. The reaction mixture was poured into ice cold water. The solid so obtained was filtered, dried and recrystallized with methanol.

2.2.5 Synthesis of title quinazolinone derivatives (K 11- K 19): A slurry consisting of 5-substituted-[1,2,4]triazolo[1,5-c]quinazolin-2-one, ethanol (5ml) and 37% formalin (1ml) was made. To this added different secondary amine (0.01mole) drop wise with cooling and shaking. The reaction mixture was allowed to stand at room temperature for 1 hour with occasional shaking, after which it was warmed on steam bath for 15 minutes. At the end of the period the contents were cooled and recrystallized from chloroform and petroleum ether.

3. Result and Discussion:

The synthesis of title compound contains five steps. 2-methyl-benzoxazin-4-one was prepared by using acetic anhydride. Treating it with semicarbazide to produce corresponding (2-methyl-4-oxo-quinazolin-3-yl)-urea; which further heated above its melting to get 5-substitued-[1,2,4]triazolo[1,5-c]quinazolin-2-one respectively. To the stirred solution of an equivalent amount of 5-methyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one and appropriated benzaldehyde in ethanol was added aqueous NaOH solution (10% w/v, 10ml). The title compounds were obtained by using formamide and different secondary amines following mannich reaction (scheme 1).

![Scheme 1]

The structures of synthesized compounds were confirmed by IR, NMR and mass spectral analysis and analytical data of synthesized compounds were shown in Table 1.
| S.No. | Comp. | Structure | Mol.Formula | Mol.wt | m.p. °C | % yield |
|-------|-------|-----------|-------------|--------|---------|---------|
| 1.    | K 11  | ![Structure](image) | C$_{22}$H$_{32}$BrN$_5$O | 452.35 | 180 | 60 |
| 2.    | K 12  | ![Structure](image) | C$_{30}$H$_{32}$BrN$_5$O | 548.43 | 180 | 50 |
| 3.    | K 13  | ![Structure](image) | C$_{22}$H$_{21}$BrN$_5$O | 465.35 | 210 | 40 |
| 4.    | K 14  | ![Structure](image) | C$_{30}$H$_{22}$N$_7$O$_3$ | 514.53 | 260 | 30 |
| 5.    | K 15  | ![Structure](image) | C$_{22}$H$_{21}$N$_7$O$_3$ | 431.35 | 220 | 34 |
| 6.    | K 16  | ![Structure](image) | C$_{22}$H$_{22}$N$_6$O$_3$ | 418.45 | 210 | 28 |
| 7.    | K 17  | ![Structure](image) | C$_{22}$H$_{22}$N$_6$O$_3$ | 418.45 | 210 | 40 |
| 8.    | K 18  | ![Structure](image) | C$_{22}$H$_{23}$N$_5$O$_2$ | 373.45 | 180 | 35 |
| 9.    | K 19  | ![Structure](image) | C$_{22}$H$_{22}$N$_5$O$_2$ | 402.45 | 200 | 35 |
5-[2-(4-bromo-phenyl)-vinyl-3-diethylaminomethyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 11)
IR (cm⁻¹): 3383.86 (NH Str), 3041.10 (CH₃ Str), 1383.69 (CO Str), 1942.95 (CH₂ bending), 1593 (NH bending), 500 (Br group).
¹H-NMR (δ ppm): 7.9-6.7 (m, 18H Ar-H ), 5.4-5.0 (2H, d, =C=CH), 3.4-3.3 (s, 2H, CH₂).
TOF MS m/z: 461 (M⁺), 269, 187, 105, 335.

5-[2-(4-bromo-phenyl)-vinyl-3-diphenylaminomethyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 12)
IR (cm⁻¹): 3459.93 (NH Str), 2359 (CN Str), 1590.43 (CO Str), 1020.09 (CH₂ bending), 1590 (NH bending), 590.04 (Br group).
¹H-NMR (δ ppm): 8.6-8.0 (m, 8H Ar-H ), 3.3-3.2 (s, 2H, CH₂), 2.56-2.54 (m, 2H, CH₂).
TOF MS m/z: 547.3 (M⁺), 335.1, 168, 170, 475.

5-[2-(4-bromo-phenyl)-vinyl-3-piperazin-1-yl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 13)
IR (cm⁻¹): 3454.01 (NH Str), 2340.82 (CN Str), 2959.5 (CH₃ Str), 1347.8 (CO Str), 1412.61 (CH₂ bending), 1593.79 (NH bending).
¹H-NMR (δ ppm): 7.9-6.7 (m, 18H Ar-H ), 5.4-5.0 (d, 2H, -C=CH₂), 3.4-3.3 (s, 2H, CH₂).
TOF MS m/z: 463 (M⁺), 105, 269, 346, 187.

5-[2-(4-nitro-phenyl)-vinyl-3-[piperazin-1-yl]-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 14)
IR (cm⁻¹): 3406 (NH Str), 3041.6 (CH₃ Str), 1706 (CN bending), 1347.8 (CO Str), 1465.61 (CH₂ bending), 1596.79 (NH bending), 1343 (NO₂ group).
¹H-NMR (δ ppm): 8.2-6.7 (m, 18H Ar-H ), 5.4-4.9 (d, 2H, -C=CH₂), 2.64-2.0 (s, 2H, CH₂).
TOF MS m/z: 513 (M⁺), 269, 105, 335, 187.

3-[(diethylamino)-methyl]-5-[2-(4-nitro-phenyl)-vinyl]-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 15)
IR (cm⁻¹): 3406 (NH Str), 2959.67 (CH₃ Str), 2341.70 (CN Str), 1347.8 (CO Str), 1254.71 (CH₂ bending), 1484.1 (NH bending), 1314(NO₂ group).
¹H-NMR (δ ppm): 8.14-7.56 (m, 8H, Ar-H), 5.6 (d, 2H, -C=CH₂), 2.40 (s, 2H, CH₂).
TOF MS m/z: 419 (M⁺), 105, 269, 187.

3-[(diethylamino)-methyl]-5-styryl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 16)
IR (cm⁻¹): 3406 (NH Str), 2959.67 (CH₃ Str), 2341.70 (CN Str), 1347.8 (CO Str), 1254.71 (CH₂ bending), 1484.1 (NH bending), 1314(NO₂ group).
¹H-NMR (δ ppm): 8.14-7.56 (m, 8H, Ar-H), 5.6 (d, 2H, -C=CH₂), 2.40 (s, 2H, CH₂).
TOF MS m/z: 419 (M⁺), 105, 269, 187.

3-[(4-nitro-phenyl)-vinyl]-5-[2-(4-nitro-phenyl)-vinyl]-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 17)
IR (cm⁻¹): 3406 (NH Str), 3041.6 (CH₃ Str), 2341.70 (CN Str), 1347.8 (CO Str), 1412.69 (OH bending).
¹H-NMR (δ ppm): 8.6-8.0 (s, 1H, NH), 7.9-7.0 (m, 9H, Ar-H), 3.6 (2H, d, d, =C=CH₂).
TOF MS m/z: 372 (M⁺), 170, 182, 187.

5-[2-(4-dihydroxy-phenyl)-vinyl-3-piperazin-1-yl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 18)
IR (cm⁻¹): 3406 (NH Str), 2959.67 (CH₃ Str), 2341.70 (CN Str), 1347.8 (CO Str), 1254.71 (CH₂ bending), 1484.1 (NH bending), 1314(NO₂ group).
¹H-NMR (δ ppm): 8.14-7.56 (m, 8H, Ar-H), 5.6 (d, 2H, -C=CH₂), 2.40 (s, 2H, CH₂).
TOF MS m/z: 419 (M⁺), 105, 269, 187.

5-[2-(4-hydroxy-phenyl)-vinyl]-3-piperazin-1-ylmethyl-[1,2,4]triazolo[1,5-c]quinazolin-2-one (K 19)
IR (cm⁻¹): 3776.09 (OH Str), 3423.88 (NH Str), 2935.51 (CH₃ Str), 2365.30 (CN Str), 1412.69 (OH bending).
¹H-NMR (δ ppm): 8.6-7.2 (m, 8H Ar-H), 6.9-6.8 (d, 2H, -C=CH₂), 2.7-2.3 (m, 4H, NC), 2.38-2.0 (s, 1H, NH), 2.0-1.9 (s, 2H, CH₂).
TOF MS m/z: 401 (M⁺), 281, 161, 229, 263.

3.1 Pharmacological activity:
3.1.1 Acute Toxicity Studies: The acute oral toxicity study was carried out as per OECD-423 guidelines. The synthesized compound was found to be non-toxic up to 2000 mg/kg body weight and did not cause any death and therefore 100 mg/kg dose level was selected.

3.1.2 Preparation of doses: The active control standard drug Diclofenac sodium and all synthesized compounds were prepared as a suspension by triturating with 1% tween 80.

3.1.3 Anti-inflammatory activity by Carrageenan induced hind Paw Oedema in rats:
The method adopted resembles essentially that described by Winter et al. Six groups of Albino rats of either sex (each comprising six animals) weighing 200 gm were deprived of food and water for 18 hours prior to experiment. The active control standard drug Diclofenac sodium and all synthesized compounds were...
administered i.p. to all the Rats. After 30 minutes 0.1 ml of 1% carrageenan sodium in normal saline was injected into sub plantar region of the paw of each rat. The edema volumes of the injected paw were measured at 0 minute, 30 minute, 1 hour, 2 hour, 3 hour, 6 hour, and 12 hour.

3.2 Statistical analysis: All values were expressed as mean ± SEM. The values obtained from the above parameters in case of synthesized compounds were compared with active control standard drug and controlled group by using one way ANOVA followed p<0.001, was considered significant.

Conclusion:
All synthesized compounds (K 11-19) resulted in good yields with 50-60%. The anti-inflammatory activity was performed at 100mg/kg body mass by rat paw oedema model.

Diclofenac sodium (100mg/kg) was used as standard.
All synthesized compounds have shown anti-inflammatory activity as all has significant reduction in inflammation when compared to inflammatory control group. Compounds K 15, K 18 and K 19 have shown very good anti-inflammatory activity comparable to standard drug Diclofenac sodium. The results were given in Table 2 and figure 2.

At 1st h compounds K 15, K 18 and K 19 showed good inhibition of inflammation when compared with other compounds. At 2nd h, all compounds have showed good inhibition of inflammation up to 12 h and shown in figure 2. These results reveals that the compounds containing piperazine and diethylamine substitution at 3rd positon of Triazolo[1,2,4]quinazolinone nucleus enhances their anti-inflammatory activities.

Table 2: Anti-inflammatory activity of synthesized compounds:

| Group                  | Compound | Dose mg/kg | Paw Volume (ml) | 0 min | 30 min | 1 hrs | 2 hrs | 3 hrs | 6 hrs | 12 hrs |
|------------------------|----------|------------|-----------------|-------|--------|-------|-------|-------|-------|--------|
| 1 Sham control         |          | 1.22±0.21  | 1.21±0.23       | 1.18±0.35 | 1.12±0.20 | 1.20±0.30 | 1.15±0.28 | 1.16±0.48 |
| 2 Inflammation control | 1%       | 0.1 ml     | 1.22±0.12       | 1.25±0.40 | 1.38±0.28* | 1.46±0.30* | 1.50±0.36* | 1.47±0.38* | 1.46±0.42* |
| 3 Active Control       | (Standard drug Diclofenac Sod.) | 50 | 1.21±0.32 | 1.24±0.42 | 1.28±0.30 b* | 1.26±0.38 b* | 1.24±0.38 b* | 1.18±0.38 b* | 1.18±0.54 b* |
| 4 Negative control     | (Vehicle Only) | 0.5 ml | 1.21±0.23 | 1.24±0.45 | 1.37±0.45* | 1.45±0.34* | 1.47±0.39* | 1.46±0.43* | 1.44±0.48* |
| 5 K 11                 | 100      | 1.21±0.32  | 1.29±0.38       | 1.35±0.38 | 1.32±0.53 b* | 1.30±0.47 b* | 1.29±0.43 b* | 1.28±0.30 b* |
| 6 K 12                 | 100      | 1.22±0.35  | 1.28±0.23       | 1.34±0.40 | 1.38±0.25 b* | 1.36±0.52 b* | 1.34±0.30 b* | 1.34±0.50 b* |
| 7 K 13                 | 100      | 1.23±0.35  | 1.29±0.48       | 1.36±0.30 | 1.39±0.42 b* | 1.35±0.36 b* | 1.32±0.36 b* | 1.31±0.38 b* |
| 8 K 14                 | 100      | 1.21±0.28  | 1.28±0.50       | 1.34±0.29 | 1.38±0.43 b* | 1.32±0.38 b* | 1.31±0.32 b* | 1.30±0.65 b* |
| 9 K 15                 | 100      | 1.20±0.25  | 1.23±0.75       | 1.29±0.48 b# | 1.27±0.38 b* | 1.26±0.39 b* | 1.24±0.28 b* | 1.22±0.43 b* |
| 10 K 16                | 100      | 1.21±0.21  | 1.23±0.29       | 1.35±0.38 | 1.31±0.32 b* | 1.27±0.40 b* | 1.23±0.40 b* | 1.21±0.45 b* |
| 11 K 17                | 100      | 1.23±0.20  | 1.26±0.65       | 1.36±0.32 | 1.35±0.38 b* | 1.29±0.30 b* | 1.28±0.58 b* | 1.28±0.56 b* |
| 12 K 18                | 100      | 1.20±0.30  | 1.23±0.67       | 1.29±0.36 b* | 1.30±0.32 b* | 1.28±0.42 b* | 1.27±0.50 b* | 1.26±0.76 b* |
| 13 K 19                | 100      | 1.22±0.32  | 1.24±0.45       | 1.29±0.38 b‡ | 1.32±0.43 b* | 1.26±0.34 b* | 1.24±0.60 b* | 1.24±0.23 b* |

a vs Sham Control, b vs Inflammatory Control, where * = p<0.0001; # = p<0.001; † = p<0.01; ‡ = p<0.05
Figure 2: Anti-inflammatory activity of all synthesized compounds.

Acknowledgements
The authors are thankful to the authorities of Division of Pharmaceutical Sciences, S.G.R.R.I.T.S. for providing necessary facilities. Authors also express our gratitude to Mr. Ravikant Incharge of animal house for providing all facilities to carry out this work. The authors are thankful to Panjab University, Chandigarh for 1H NMR spectral data and Mass spectral data.

References:
1. Georgey H, Abdel-Gawad N, Abbas S. Synthesis and Anticonvulsant activity of some Quinazolin-4-(3H)-one Derivatives. Molecules 2008; 13:2557-2569.
2. Ilangovan P, Ganguly S. Design and Synthesis of Novel Quinazolinone Derivatives as Broad Spectrum Anticonvulsant and Antimicrobial Agent. J Pharm Research 2010;3:703-706.
3. Bhandari SV, Deshmame BJ, Dangare SC, Gore ST, Raparti VT, Khachane CV, Sarkate AP, et al. Anticonvulsant activities of some novel 3-[5-substituted 1, 3, 4-thiadiazole-yl]-2-styryl Quinazoline-4(3H)-ones. Pharmacologyonline 2008; 2:604-613.
4. Patel NB, Patel JC, Barat GG. Synthesis and antimicrobial activity of pyrazolyl-quinazolin-4(3H)ones. Der Pharma Chemica 2009; 1:228-238.
5. Havaldar FH, Patil AR. Syntheses of 1, 2, 4 Triazole Derivatives and their Biological Activity. E J Chem 2008; 5:347-354.
6. Siddappa K, Reddy T, Mallikarjun M, Reddy CV, et al. Synthesis, Characterization and Antimicrobial Studies of 3-[(2-Hydroxy-quinolin-3-ylmethylene)-amino]-2-phenyl-3H-quinazolin-4-one and its Metal(II) Complexes. E J Chem 2008; 5:155-262.
7. Ravichandran V, Mohan S, Kumar KS. Synthesis and antimicrobial activity of Mannich bases of isatin and its derivatives with 2-[(2,6-dichlorophenyl)amino]phenylacetic acid. ARKIVOC 2007; 51-57.
8. Mistry BD, Desai KR, Patil JA. Synthesis and Antimicrobial activity of newer Quinazolinones. E J Chem 2006; 3:97-102.
9. Mohamed MS, Kamel MM, Kassem EMM, Abotaleb N, Nofal SM, Ahmed MF, et al. Novel 3-(p-substituted phenyl)-6-bromo-4(3H)-Quinazolinone Derivatives of promising anti-inflammatory and analgesic properties. Acta Polonae Pharmaceutica-Drug Research 2009; 66: 487-500.
10. Chandra T, Garg N, Kumar A. Synthesis of Sulpha Drug Quinazolin -4-one Derivatives and their Evaluation for Anti-inflammatory Activity. World J Chem 2009;4:210-218.
11. Laddha SS, Wadodkar SG, Meghal SK. Studies on some biologically active substituted 4(3H)-quinazolinones. Part 1. Synthesis, characterization and antiinflammatory –antimicrobial activity of 6,8-disubstituted 2-Phenyl-3-[substituted-benzothiazol-2-yl]-4(3H)-Quinazolinones. ARKIVOC 2006; 11:1-20.
12. Kandu SK, Mathew PD, Maritza V, Mahindaratne, Bao A, Negrete GR, et al.
One-pot reductive cyclization to antitumor quinazoline precursors. ARKIVOC 2008; 33-42.

13. Cipak L, Repicky A, Jantova S. Growth Inhibition And Apoptosis Induced by 2-Phenoxymethyl-3H-Quinazolin-4-One in HL-60 Leukemia Cells. Exp Oncol 2007; 29:13-17.

14. Alagarsamy V, Thangathiruppathy A, Mandal SC, Rajasekaran S, Kumar SV, Revathi R, Anburaj Kumar SA, Rajesh S, et al. Pharmacological Evaluation of 2-substituted (1,3,4) thiadiazolo Quinazolines. Ind J Pharm Sci 2006;68:108-111.

15. Zyl V, Etienne F. A survey of reportedsynthesis of Methaqualone and some positional and structural Isomers. For Sci Int 2001; 121:142-149.

16. Shetty BV. A review on a novel Quinazolone Diuretic Zaroxolyn (Metolazone). Ind J Pharmace 1974; 6:40-53.

17. Gao X, Cai X, Yan K, Song B, Gao L, Chen Z, et al. Synthesis and Antiviral bioactivities of 2- methyl -3-substitued-benzalamino-4(3H)-Quinazolinone derivatives. Molecule 2007; 12:2621-2642.

18. Campbell SF, Davey MJ, Hardstone JD, Lewis BN, Palmer MJ, et al. 2,4-Diamino-6,7-dimethoxyquinazolines. 1. 2-[4-(1,4-benzodiaxan-2-yl carbonyl) piperazin-1-yl] Derivatives as α1-Adrenoreceptor antagonists and antihypertensive agents. J Med Chem 1987;30:57-62.

19. Kajavi MS, Montazari N, Hosseini SSS. Reaction of anthranilic acid with Orthoesters: A new facile one-pot synthesis of 2-substituted 4H-3,1-Benzoxazin-4-ones. J Chem Research 1997; 288-287.

20. Winter CA, Risley EA, Nuss GW. Carregeenan-induced oedema in hind paws of the rat as an assay for anti-inflammatory. Proc Soc Exp Biol Med 1962; 3:111:544-547.