Available online on 15.08.2020 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Synthesis And Anagesic activities of Quinazolin-4(3H)-One, 2-Methyl-4(3H)-Quinazolinone and 2–Phenyl-4(3H)-quinazolin-4(3H)–one

P.O. Osarumwense*[1], M.O. Edema[2], and C.O. Usifoh[3]

*[1]Department of Chemical Sciences, Ondo State University of Sciences and Technology, Okitipupa, Ondo State, Nigeria

[2]Provost Office, College of Education, Warri, Delta State, Nigeria

[3]Faculty of Pharmaceutical Chemistry, University of Benin, Benin City, Nigeria

ABSTRACT

Background: Objective: The current study is aimed at the synthesis of these quinazolinone derivatives quinazolin-4(3H)-One, 2-Methyl-4(3H)-quinazolinone and 2–Phenyl-4(3H)-quinazolin-4(3H)–one and evaluate them for their analgesic activity. **Method:** The condensation of 2-amino-methyl-4-methoxybenzoate with acetic anhydride yielded the cyclic compound 2-methyl-4, 5-disubstituted-1, 3-benzo-oxazine-4-one which further produce a novel 2,3-disubstituted quinazolin-4 ones via the reaction with hydrazine hydrate The quinazolinone derivatives quinazolin-4(3H)-One, 2-Methyl-4(3H)-quinazolinone and 2–Phenyl-4(3H)-quinazolin-4(3H)–one were evaluated pharmacologically for their in vivo analgesic activities by acetic acid induced writhing in mice. The compounds synthesized were unequivocally confirmed by means of Infrared, Nuclear Magnetic Resonance (^{1}H and ^{13}C), Gas Chromatography Mass Spectrophotometer and Elemental analysis.The synthesized compounds were screened for their analgesic activity.Compounds 1,2 and 3 showed significant analgesic activity. **Discussion:** Compound 1 was characterized by the absence of methyl group and the presence of methyl group for compound 2. The test investigated compounds exhibited significant analgesic activity when compared with the control test sample. The compounds synthesized exhibited promising analgesic activities against . **Conclusion:** The compounds have high analgesic activity. Compound 3 has a higher activity compared to Compound 2 and compound 2 has a higher analgesic activity compared to compound 1. Compound 3 has a higher analgesic activity compared to the standard drugs Aspirin and Indomethacin.

Keywords: quinazolin-4(3H)-One, 2-Methyl-4(3H)-quinazolinone and 2–Phenyl-4(3H)-quinazolin-4(3H)–one quinazolin-4(3H)-one, analgesic activity.

Article Info: Received 18 June 2020; Review Completed 21 July 2020; Accepted 28 July 2020; Available online 15 August 2020

Cite this article as:

Osarumwense PO, Edema MO, Usifoh CO, Synthesis And Anagesic activities of Quinazolin-4(3H)-One, 2-Methyl-4(3H)-Quinazolinone and 2–Phenyl-4(3H)-quinazolin-4(3H)–one, Journal of Drug Delivery and Therapeutics. 2020; 10(4-s):87-91 http://dx.doi.org/10.22270/jddt.v10i4-s.4209

***Address for Correspondence:**

P.O. Osarumwense, Department of Chemical Sciences, Ondo State University of Sciences and Technology, Okitipupa, Ondo State, Nigeria

1. INTRODUCTION

Pain in community-dwelling adults is a major public health problem. Epidemiologic studies estimate that the prevalence of chronic pain in the general population ranges from 7% to 55% [1-6]. Regrettably, people in pain must often make difficult choices about pain relief therapy, because most treatment options for pain management include the use of analgesics and adjuvant medications that may have adverse side effects, are often unavailable or costly, or trigger fears of addiction. A few studies have examined the attitudes of the public toward pain in general, but research on the factors contributing to the undertreatment of pain is lacking.[1,4].

An analgesic, or painkiller, is any member of the group of drugs used to achieve analgesia-relief from pain [5]. Analgesic drugs act in various ways on the peripheral and central nervous systems. They are distinct from anesthetics, which reversibly eliminate sensation, and include Paracetamol [known in the US as Acetaminophen or simply APAP], the non-steroidal anti-inflammatory drugs [NSAIDs] such as the salicylates, and opioid drugs such as morphine and opium. In choosing analgesics, the severity and response to other medication determines the choice of agent; the World Health Organization [WHO] pain ladder [6]. Analgesia due to blockade of pain nerve sensitizing mechanism induced by bradykinin, TNFα, ILs [7].

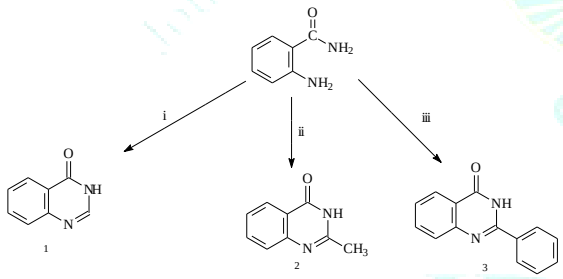
Literature survey revealed the versatile biological activities of quinazolinone derivatives [8]. It has been established that quinazolinones possess antiviral [9], antifungal[10], antiallergic[11], antitumor [12], and antidiabetic activities [13]. In the recent past, quinazolinones were reported to exhibit pronounced coronary vasodilatory [14] and histamine receptor type 3

inverse agonism [15]. Various researchers have reported the antibacterial activity of quinazolinone derivatives [15–19].

Quinazolinone and their derivatives are building block for approximately 150 naturally occurring alkaloids isolated from a number of families of the plant kingdom, from microorganisms and animals. In light of the growing number of applications in recent years, there has been an enormous increase in the interest among biologists and chemists in their synthesis and bioactivity of quinazolinone derivatives. Compounds containing 4(3H)-quinazolinone ring system have showed antitumor, anticonvulsant, antitubercular activities, anti-inflammatory, analgesic, antimicrobial and anticoccidal activities [20 - 24].

Quinazolinones have been frequently used in medicine [25 - 27], such as quinethazone and metolazone and are used in medicine as diuretics while prazosin is a vasodilator, which is also used as asn antihypertensive drug. Quinazolinones are also a class of drugs which function as hypnotic/sedatives that contain a 4-quiazolinone core. Their use has also been proposed in the treatment of cancer [28]. Examples include afloqualone, cloroqualoneand diproqualone.

The synthesized compounds were screened for their analgesic activity using the acetic acid induced abdominal constriction method which is widely used for the evaluation of peripheral antinociceptive activity. The compounds synthesized display analgesic activity. Compounds 1, 2, and 3 showed significant analgesic activity.



Scheme 1

i=$HC(OC_2H_5)_3$, ethanol,

ii=$CH_3C(OC_2H_5)_3$, ethanol,

iii=$C_6H_5C(OC_2H_5)_3$, ethanol.

2. MATERIALS AND METHODS

General Experimental Procedure

Reagents and solvents were purchased from sigma-Aldrich chemical supplier in Germany. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Buck scientific IR M500 instrument. The ^1H and ^{13}C NMR spectra were recorded in DMSO-*d*6 at 400MH_z with HAZ VOLATILE V2.M. Chemical shifts are reported in ppm relative to tetramethylsilane period. Gas chromatography mass (GC/MS) spectra were obtained on a Finingan MAT 44S mass spectrometer operating at electron impact energy of 70eV. Elemental analysis data agreed with the calculated values. Analytical thin layer Chromatography (TLC) was used to monitor the reactions.

Synthesis Of 4-(3h)-Quinazolinone (1)

Anthranilamide 0.68g (0.005mol) and triethyl orthoformate 0.74g (0.005mol) were refluxed in 20ml ethanol with stirring using a magnetic stirrer until TLC indicated complete disappearance of the starting material (2 hours). The resulting solution was concentrated in vacuum and extracted into dichloromethane. The organic layer was dried over anhydrous sodium sulphate filtered and evaporated to give solid products which were recrystallized from Dimethylformamide (DMF), 0.66g (97%), mp 215-217^oC.

Synthesis Of 2-Methyl-4(3h)-Quinazolinone (2)

Anthranilamide 0.68g (0.005mol) and triethyl orthoacetate 0.81g (0.005mol) were reacted following the procedure for 1 above. Yield was 0.64g (94%), mp: 231-233^oC.

Synthesis Of 2-Phenyl-4 (3H)-Quinazolinone (3)

Anthranilamide 0.68g (0.005mol) and triethyl orthobenzoate 1.12g (0.005mol) were were reacted following the procedure for 1 above. Yield was 0.57g (83%), mp: 198-200^0C.

Pharmacological Evaluation

Swiss mice (18-23g) of both sexes were used. The animals were maintained under standard diet Sand water. Test compounds were administered orally at dose levels. Ethics committee of the Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Analgesic activity

The acetic acid induced abdominal constriction method is widely used for the evaluation of peripheral antinociceptive activity [29] (Gene et al., 1998). It is very sensitive and able to detect antinociceptive effects of compounds at dose levels that may appear inactive in other methods like the tail-flick test (collier et al., 1968. Bentley et al., 1981) [30, 31]. Local perietoneal receptors are postulated to be partly involved in the abdominal constriction response (Bentley et al., 1983) [32]. The method has been associated with prostanoids in general, e.g increased levels of PGE2 and PGE2a in peritoneal fluids (Derardt et al., 1980) [33], as well as lipoxygenase products by some researchers (Levini et al., 1984), Dhara et al., 2000)[34, 35]. Indomethaan (10mg/kg) was administered orally as reference drug while 10% olive oil was used as negative

Statistical analysis

All data were expressed as the mean + SEM, the students't-test was applied to determine the significance of the difference between the control group and the test compounds.

3- RESULTS

Table 1: Characterization and physical data of synthesized compounds

Compound No	Solvent	Formula M. wt	Analysis % Calc/Found C	H
1	Ethanol	$C_{11}H_{11}N0_4$	62.20	5.18
		(221.209)	62.10	4.98
2	Ethanol	$C_{11}H_{13}N_30_3$	56.11	5.53
		(235.239)	56.40	5.41
3	Ethanol	$C_{11}H_{13}N_30_3$	56.11	5.53
		(235.239)	56.40	5.41

Table 2: ^{13}C-NMR of Synthesized compounds

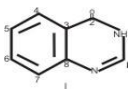
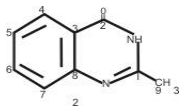
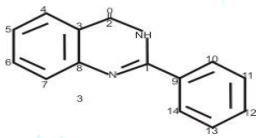
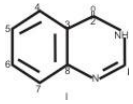
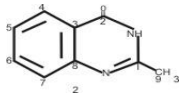
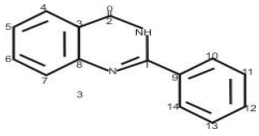
Compound No	δ (ppm) Carbon atom number
1 	168.28(C-2), 155.80(C-6), 149.23(C-8) 140.28 (C-1), 113.37 (C-5), 100.56 (C-4) 100.05 (C-3), 100.01 (C-7), 16.95 (C-9) 56.13 (C-10), 51.93 (C-11)
2 	160.28 (C-2), 155.29 (C-6), 154.57 (C-1) 149.07 (C-8), 143.77 (C-5), 113.65 (C-1) 108.24 (C-3), 105.64 (C-7), 56.80 (C-10) 56.63 (C-11), 22.58 (C-9)
3 	168.28(C-2), 155.80(C-6), 149.23(C-8) 140.28 (C-1), 113.37 (C-5), 100.56 (C-4) 100.05 (C-3), 100.01 (C-7), 16.95 (C-9) 56.13 (C-10), 51.93 (C-11)

Table 3: ^{1}H-NMR of Synthesized compounds

Compound No	δ (ppm) Carbon atom number
1 	7.74 (s, 1H), 7.55 (d, 1H), 7.16 (t 1H), 7.08 (s, 1H), 6.70 (d 1H), 6.40 (s, 1H), 3.78 (t 1H) 3.68 (s, 1H).
2 	7.41 (s, 1H), 7.10 (d, 1H), 7.09 (t 1H), 7.08 (s, 1H), 6.70 (d 1H), 6.58 (s, 1H), 5.80 (t 1H) 2.56 (s, 1H),
3 	8.22 (d, 1H), 7.88 (t, 1H), 7.76 (d, 1H), 7.60 (t, 1H), 7.53 (d, 3H), 5.71 (s, 2H), 3.38

Characterization of **4-(3H)-Quinazolinone (1)**

^{1}H NMR (400 MHz, DMSO) δ 7.74 (s, 1H), 7.55 (d, 1H), 7.16 (t 1H), 7.08 (s, 1H), 6.70 (d 1H), 6.40 (s, 1H), 3.78 (t 1H) 3.68 (s, 1H), ^{13}C NMR (400 MHz,) δ 172.18, 151.06, 132.75, 129.63, 117.30, 115.26, 114.63, 40.43, 1R (KBr,cm^{-1}), 3387 (NH_2), 2871, 2781 (CH aliphatic), 1700 (C=0). Anal Cal. for $C_8H_6N_20$: C 66.12, H 4.13, Found: C 67.42 H 4.99.

Characterization of **2-Methyl-4(3h)-Quinazolinone (2)**

^{1}H NMR (400 MHz, DMSO) δ 7.41 (s, 1H), 7.10 (d, 1H), 7.09 (t 1H), 7.08 (s, 1H), 6.70 (d 1H), 6.58 (s, 1H), 5.80 (t 1H) 2.56 (s, 1H), ^{13}C NMR (400 MHz,) δ 168.28, 151.06, 132.75, 129.63, 117.30, 115.26, 100.5, 56.13, 51.93, 16.92. 1R (KBr,cm^{-1}), 3252, 3325, 3345 (NH_2),1641 (C=N), 3015 (CH, aromatic), 1693 (C=0). Anal Cal. for $C_9H_8N_20$: C 67.42, H 4.99, Found: C 68.96 H 4.77.

Characterization of **2-Phenyl-4 (3H)-Quinazolinone (3)**

^{1}H NMR (400 MHz, DMSO) δ 8.22 (d, 1H), 7.88 (t, 1H), 7.76 (d, 1H), 7.60 (t, 1H), 7.53 (d, 3H), 5.71 (s, 2H), 3.38 (s, 1H) ^{13}C NMR (101 MHz, DMSO) δ 162.08, 156.67, 147.61, 135.79, 120.97, 1R (KBr,cm^{-1}), 3387 (NH) 1697 (C=0). Anal Cal. for $C_{14}H_{10}N_20$: C 75.61, H 4.50, Found: C 75.10 H 4.11.

Table 4: Effect of the Synthesized Compounds on acetic acid induced writhing in mice (Analgesic activity of the compounds synthesized relative to control)

Compounds No.	Doses mg/kg (P.O)	Numbers of writhing (per 20min)	% Inhibition
1	20	36.11 ± 0.18	47.67
	40	20.42 ± 2.45	70.41
2	20	27.56 ± 1.16	60.06
	40	16.01 ± 0.22	76.80
3	20	22.01 ± 0.18	68.10
	40	14.11 ± 0.48	79.55
Aspirin,		22.50 ± 3.07	67.39
Indomethacin	10	14.80 ± 4.95	78.55

Values are mean $\pm$ S.E.M; $P < 0.001$, significantly different from control, paired t-test ($n = 5$), P. O = per oral.

4. DISCUSSION

The reaction of Anthranilamide and triethyl orthoformate (1), triethyl orthoacetate (2) and triethyl orthobenzoate (3) yielded the quinazolinone derivatives quinazolin-4(3H)-One (1) 2-Methyl-4(3H)-quinazolinone (2) and 2–Phenyl-4(3H)-quinazolin-4(3H)–one (3). These compounds were evaluated pharmacologically for their in vivo analgesic activities by acetic acid induced writhing in mice.

Structural elucidations of compounds synthesized were characterized by correct elemental analysis and careful inspections of spectral data. Looking at the ^{1}H NMR spectra of the compounds synthesized, compound 2 displayed a singlet signal at: δ 3.68 attributed to methyö group which was absent in compound 1. Other singlets appeared at δ 7.74, 7.55, 7.16, and 7.08 for compound 1, attributed to aromatic protons. The ^{13}C NMR spectrum for compound 1 showed 11 peaks that represented the C atoms in the compound. This confirmed the structure of the compound as there were 11 non-equivalent carbon atoms in the compound. All the carbon atoms appeared at a high chemical shift values, and occurred between 100.01-168.28 confirming that they are unsaturated C. The >C=O is characteristically at 168.28.

The ^{1}HNMR of compound 1 revealed seven protons. One of the protons at chemical shift 2.54ppm is attributed to the solvent DMSO. All the peaks were singlets. The singlet at position 11.45ppm is attributed to NH proton, while the signals at positions 7.78ppm, 7.55ppm, 7.16ppm, and 7.08ppm are all due to aromatic protons.

Also, ^{1}H NMR spectrum of compound 2 showed a characteristic signal at δ 2.56 (singlet) corresponding to methyl group. Two singlets appeared at δ7.41 and 7.10 attributed to aromatic protons. Another signal appeared at 5.80 which was attributed to the protons of the amino group. For the IR spectra, compound 2 was characterized by absence of υ C-0 and presence of υNH_2 in 3301cm^{-1}and 3300 region of the compounds.

The ^{13}C NMR spectrum of compound 1, revealed signals at δ16.95, 51.93 and 56.13 attributed to methyl groups respectively, while the aromatic carbon atoms appeared between δ values 100.05-168.28 with the carbonyl carbon atom appearing as the highest δ value of 168.28. Similarly, compound 2 showed signals at δ22.58, 56.63 and 56.80 attributed to methyl and the two methoxy groups respectively, while the aromatic carbon atoms appeared between δ values 105.64-160.28, with the carbonyl carbon atom appearing as the highest δ value of 160.28.

The ^{13}C nuclear magnetic resonance revealed low δ values for the aliphatic carbons. This is because the alkyl group is electron donating and hence produces a shielding effect which makes the carbon atom to resonate at low δ values. The aromatic and the carbonyl carbon atoms appeared at high δ values. This is because the aromatic ring is electron withdrawing and the aromatic carbons are highly deshielded and resonate at high frequency. The electronegative effect of the oxygen atom on the carbonyl group makes the carbonyl carbon to appear at higher δ value.

This present study reported the synthesis of these three compounds and they were investigated for their analgesic activity. The compounds synthesized exhibited promising analgesic activity. Compound 1 has analgesic activity of 47.67% and 70.41% at 20mg/kg and 40mg/kg respectively, while compound 2 has analgesic activity of 69.06% and 76.80%at 20mg/kg and 40mg/kg respectively. Compound 3 has activity of 68.10% and 79.55%. Compound 3 showed the highest activity at 40mg.kg of 79.55% growth Inhibition compared to the other compound 1, compound 2, acetylsalicylic acid and indomethacin. It may be that the substitution of Amino group at position three increase the activity. These compounds synthesized have a higher analgesic activity than acetylsalicyclic acid, which is a standard analgesic drug. These three compounds exhibited promising analgesic activity. In addition, compound 1 showed analgesic activity of while compound 2 . This indicated that compound 3 was active against four microorganisms compared to compound 1 and 2 which were only active against three microorganism. Compound 3 showed the highest activity compared to compound 2, while compound 2 has a higher analgesic activity compared to compound 1.

5. CONCLUSIONS

Although numerous classes of quinazolinones have been synthesized their syntheses have the disadvantage of being multiple step reactions and time taken which are in hours and sometimes in days. However, the synthetic pathways in this study have numerous benefits for performing synthesis in organic compounds including reduced pollution, increased reaction rates, yield enhancement and cleaner chemistries.

The present study has shown that the quinazolinone derivatives 1, 2 and 3 have analgesic activity with Compound 2 showing a higher activity compared to compound 1 and 3.

Conflict of interest

The authors declare no conflict of interest.

Authors' declarations

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

The authors appreciate the assistance of Dr. Marvis E. in England for running the spectra and the Department of Pharmaceutical Microbiology, Faculty of Pharmacy, University of Benin for providing the test organisms.

REFERENCES

1. Crook J, Rideout E, Browne G. The prevalence of pain complaints in a general population. Pain 1984; 18(3):299–314.
2. Levin DN, Cleeland CS, Dar R. Public attitudes toward cancer pain. Cancer 1985; 56:2337–2339.
3. Eggen AE. The Tromsø Study: frequency and predicting factors of analgesic drug use in a freeliving population (12–56 years). J Clin Epidemiol 1993; 46(11):1297–1304.
4. Bostrom M. Summary of the Mayday Fund survey. J Pain Symptom Manage 1997; 13:166–168.
5- Tambaro S, Reali R, Volonterio A, Zanda M, Olimpieri F, Pinna GA, Lazzari P, NESS002 ie: A new fluorinated thiolendopeptidase inhibitor with antinociceptive activity in an animal model of persistent pain, Pharmacology, Biochemistry and Behavior, 2013; 1-7.
6. Harper D [2001]. Online Etymology Dictionary: Analgesia. Retrieved December 3:2012.
7. Deng JS, Chi CS, Huang SS, Shie PH, Lin TH, Huang GJ. Antioxidant, analgesic, and anti-inflammatory activities of the ethanolic extracts of Taxillus liquid ambaricola, Journal of Ethnopharmacology 2011; 137:1161– 1171.
8. Büyüktimkin S. Synthesis, pharmacology and structure-activity relationships of 2-methyl-3-(4-oxo-3-phenyl-thiazolidin-2-ylidenamino)- 4(H)-quinazolinone derivatives. Arch Pharm. 1985; 318:496–501.
9. Büyüktimkin S, Büyüktimkin N, Özdemir O, Rollas S. Synthesis of 3-[2-(2,3-dihydro-5-phenyl-4-substituted-3H-1,2,4-triazole-3-thione2-yl)-acetylamino]-2-methyl-4(3H)-quinazolinones and their pharmacological activities. Arch Pharm. 1989; 322:49–52.
10. Mukherji DD, Nintiyal SR, Prasad CR, Dhawan BN. Pharmacological studies on quinazolinones. Ind J Med Res. 1980; 93:1426–1432.
11. Peet NP, Baugh LE, Sunder S, et al. 3-(1H-tetrazol-5-yl)-4(3H)-quinazolinone sodium salt (MDL 427): a new anti-allergic agent. J Med Chem. 1986; 29:2403–2409.
12. Chaurasia MR, Sharma SK. Synthesis of some new 4(3H)-quinazolinones as a potent CNS depressant. Arch Pharm. 1982; 315:377–381.
13. Li H, Wang JP, Yang F, et al. Design, synthesis and biological activity evaluation of 2-mercapto-4(3H) quinazolinone derivatives as a novel inhibitor of protein tyrosine phosphatase 1B. Heterocycles. 2012; 85:1897–1911.
14. Chiou WF, Liao JF, Chen CF. Comparative study on the vasodilatory effects of three quinazoline alkaloids isolated from Evodia rutaecarpa. J Nat Prod. 1996; 59:374–378.
15. Nagase T, Mizutani T, Ishikawa S, et al. Synthesis, structure-activity relationships, and biological profiles of a quinazolinone class of histamine H3 receptor inverse agonists. J Med Chem. 2008; 51:4780–4789.
16. Nanthakumar R, Muthumani P, Girija K. Anti-inflammatory and antibacterial activity study of some novel quinazolinones. Arabian J Chem. 2014; 7:1049–1054.
17. Khodarahmi GA, Khajouel MR, Hakimelahi GH, Abedi D, Jafari E, Hassanzadeh F. Antibacterial, antifungal and cytotoxic evaluation of some new 2,3-disubstituted 4(3H)-quinazolinone derivatives. Res Pharm Sci. 2012; 7:151–158.
18. Hemalatha K, Girija K. Synthesis, characterization, preliminary QSAR studies and in vitro antioxidant activity of some novel 2,3-disubstituted quinazolinone derivatives. Int J Pharm Sci. 2012; 4:99–103.
19. Panwar H, Chaudhary N, Singh S, Singh SH. Anti-inflammatory and antimicrobial activity of some new quinazolinones. Rasayan J Chem. 2011; 4:498–505.
20. Cao SL, Feng YP, Jiang YY. Synthesis and in vitro antitumor activity of 4(3H)-quinazolinone derivatives with dithiocarbamate side chains. Bio Org Med Chem 2005; 15:1915-1917.
21. Giri RS, Thaker HM, Giordano T, Williams J. Design, synthesis and characterization of novel 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3Hquinazoline-4-one derivatives as inhibitors of NF-kappaB and AP-1 mediated transcription activation and as potential anti-inflammatory agents. European J Med Chem 2009; 44:2184–2189.
22. Helby, Abdel MH. Design and synthesis of some new derivatives of 3Hquinazolin-4-one with promising anticonvulsant activity. Acta Pharma 2003; 53:127–138.
9123. Kadi AA, Azab AS, Alafeefy AM, Abdel SG. Synthesis and biological screening of some new substituted 2-mercapto-4(3H)quinazolinone analogues as anticonvulsant agents. J. Pharma. Sci. 2006; 34:147-158.
24. Jatav V, Mishra P, Kashaw S. CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones. European J Med Chem 2008; 43:1945-1951.
25. Xia Y, Yang ZY, Hour MJ, Kuo SC. Antitumour agents.Part 204: Synthesis and biological evaluation of substituted 2-aryl quinazolinones. Bioorg Med Chem Lett 2001; 11:1193–1196.
26. Jessy EM, Sambanthan AT, Alex J, Sridevi CH, Srinivasan KK. Synthesis and biological evaluation of some novel quinazolones. Indian J Pharm Sci 2007; 69:476-478.
27. Alagarsamy V, Thangathiruppathy A, Mandal SC, Rajasekaran S. Pharmacological evaluation of 2-substituted (1,3,4) thiadiazolo quinazolines. Indian J Pharm Sci 2006; 68:108-111
28. Chen K, Wang K, Kirichian AM et al. In silico design, synthesis, and biological evaluation of radioiodinated quinazolinone derivatives for alkaline phosphatasemediated cancer diagnosis and therapy. Mol Cancer Ther 2006; 5:3001–13.
29. Gene, R.M; Segura, L.; Adzet, T.; Marin, E.; inglesias, J. Heterotheca inuloides: *Journal of ethnopharmacology*. 1998; **60**:157-162.
30. Collier H.O.J; Dinneen L.G.; Johnson C.A.; and Schneider C. The abdominal constriction response and its suppression by analgesic drugs in the mouse. *Brit J. Pharmacol.* 1968; **32**:295-310.
31. Bentley G.A; Newlon S.H.; and Starr J. Evidence for action of morphine and Enkephalins on sensory nerve ending in the mouse peritoneum *Br. J. Pharmacol* 1981; **73**:325-332.
32. Bentley K.W. The Isoquinolin Alkaliods, pergamon, press London, *Comprehensive Medicinal Chemistry Pergamon press; Oxford.* 1983. 2016. - V. 18, l. 16. - P. 4475-4525.
33. Derardt R, Jongney S, Delvalcee F. and Falhout, M. Release of protagladdins E and F in an analgesic reaction and its inhibition. *Eur. J. Pharmacol.* 1980; 51:17-24.
34. Levini J.D., Lau W., Kwait G. and Goetal E.J. Leukotriene B4 produces hyperanalgesia that is dependent on the polymorphonuclear leucocytes. *Science.* 1984; 225:743-745.
35. Dhara A.K, Suba V, Sen T, Pal S. and Chaudhuiri A.K. Preliminary studies on the anti-inflammatory and analgesic activity of methanolic fraction of the root of *Tragia involucrate. J. Ethnopharmacol.* 2000; 72:265-268.