BEST: Journal of Recent Trends in Pharmacology, Medical Microbiology & Toxicology (BEST: JRTPMMT)
Vol. 1, Issue 1, Dec 2016, 7-20

A REVIEW ON BIOLOGICAL ACTIVITIES OF QUINOLINE DERIVATIVES

SHARMA POONAM, KAUR KAMALDEEP, CHAWLA AMIT, SINGH RANJODH, & SINGH RAHULDEV DHAWAN R. K

Khalsa College of Pharmacy, Amritsar, Punjab, India

ABSTRACT

Quinoline and its derivatives have diverse biological activities and this functional moiety perform an important class of derivatives for the development of new drug. So many researchers have designed, synthesized and tested its biological activities on various target. Quinoline derivatives commonly used in myocardial infarction which is resulting from acute coronary occlusion (ischemia) reduces survival and leads to deterioration of the quality of life and restoration of blood flow. This restoration of blood flow after transient ischemia leads to detrimental changes such as arrhythmias, enzyme release, or severe intra-myocardial hemorrhage and this condition is known as Myocardial Ischemia Reperfusion Injury. In 1820, cinchona was extracted and quinine was isolated from this plant was widely used as active ant malarial agent. Further some more derivatives were derived like 8-hydroxy quinoline derivatives. Quinoline derivatives/compounds also reported as antiplasmodial, cytotoxic, ant proliferative, antibacterial, anticancer, antitubuerculosis and antimalarial.

KEYWORDS: Antimalarial, Quinoline, Cytotoxic, Antibacterial

INTRODUCTION

Chemical names of quinoline are benzo-pyridine or 1-aza-napthalene. These are weak tertiary base with alkaloidal nature and contain nitrogenous heterocyclic aromatic ring. Quinoline has molecular formula: C_9H_7N and 129.16: mol. wt. Quinoline nucleus gives same reactions of pyridine and benzene. The main chemical reactions are nucleophilic and electrophonic substitution in nature.

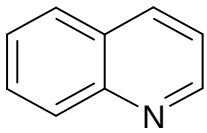


Figure 1: Quinoline (1-Aza Naphthalene)

Quinoline derivatives commonly used in myocardial infarction which is resulting from acute coronary occlusion(ischemia) reduces survival and leads to deterioration of the quality of life and restoration of blood flow through thombolysis, percutaneous transluminal coronary angioplasty, and coronary bypass surgery and cardiac transplantation becomes prerequisite to salvage this ischemic myocardium but the restoration of blood flow after transient ischemia leads to detrimental changes such as arrhythmias, enzyme release, or severe intra-myocardial hemorrhage and this condition is known as *Myocardial Ischemia Reperfusion Injury* (David Garcı´a-Dorado *et al.,2003*).

The pathogenesis of ischemia–reperfusion injury was explained on the basis of two main hypotheses, namely oxidative stress and Ca-overload (Dhalla NS *et al.*, 1996; Ferrari *et al*., 1996; Griendling*et al*., 1997; Kaplan *et al.*, 1997). Both these mechanisms are related to each other. Oxidative stress is associated with increased formation of reactive oxygen

species (ROS), modifies phospholipids and proteins leading to lipid peroxidation and oxidation of thiol groups which leads to alteration of membrane permeability and modification of various cellular proteins. (Ceconi*et al*., 1991; Dhalla NS *et al*., 1996). Oxidative stress produces cellular defects including a depression in the sarcolemmal (SL) Ca –pump ATPase and Na –K ATPase activities which leads to decreased Ca -efflux and increased Ca -influx after ischemia (Ferrari *et al*., 1985; Garlick*et al*., 1987; Grech*et al*., 1996; Kato *et al*., 1998; Mitsos*et al*., 1986; Musat*et al*., 1996; Slezak*et al*., 1995)**.** Alterations in the myocardium during ischemia–reperfusion are a part of oxidative stress associated with depressed contractile function as indicated by decreased left ventricular developed pressure (LVDP), 1d*P*/d*t*(rate of pressure development), 2d*P*/d*t*(rate of pressure decline) and increased left ventricular end-diastolic pressure (LVEDP).

Quinoline has been found to possess various biological activities. Some of them are as follows:

Antimalarial: Quinolines are well known for their antimalarial potential. Bisquinolines that possesses antimalarial activity against both chloroquine-resistant and chloroquine sensitive parasites were developed (Rayne*set al*., 1996). Chibale*et al* found that analogues of ferrochloroquine have antimalarial activity (Chibale*et al*., 2000) certain 7-chloroquinolinyl thioureas were synthesized and estimated for their ant malarial activity (Mahajan*et al.,* 2007*)*. Ureido-4-quinolinamides were synthesized which possessed antimalarial effect at MIC of 0.25 mg/mL against chloroquine-sensitive plasmodium falciparum strain (Modapa*et al*., 2009). Kovi*et al*., synthesized chloroquinolyl derivative which showed potent ant malarial activity at submicromolar levels (Kovi*et al*., 2009).

Analgesic: 4-Substituted-7-trifluoromethylquinolines synthesized that showed good analgesic activity and nitric oxide releasing properties (Abadi*et al*., 2005). Manera*et al*. synthesized a few quinoline derivatives which act as selective agonists at Cannabinoid CB2 receptors and showed analgesic activity (Manera*et al*., 2007).

Antiprotozoal: 2-substituted quinoline alkaloids isolated from G. longiflora plant and used for the treatment of new world cutaneous leishmaniasis (Fournet*et al*., 1993). Alkenyl and alkynylquinolines were synthesized that showed activity against the causative agents of cutaneous leishmaniasis, Visceralleishmaniasis, African trypanosomiasis and Chagas' disease (Fakhfakh*et al*., 2003). Ma *et al*., developed certain quinolones that possesses activity against *Trypanosomacruzi.* (Ma *et al*., 2009).Franck *et al*., developed quinoline derivatives which are active against *T. cruzi*(Franck *et al*., 2004).

Anthelmintic: Substituted 2, 4-arylquinolines synthesized that have a good activity against the nematode *Haemonchuscontortus*. These arylquinolines also showed activity against levamisole, ivermectin and thiabendazole resistant strains of *H. contorts* (Rossiter*et al*., 2005)

Also quinoline ring has been found to possess *anti-bacterial, antifungal, anticonvulsant, anti-inflammatory, antiviral, hypoglycemic, reproductive, antineoplastic activity*, etc. (Marella*et al.,* 2012)but our sake of interest is the use of quinoline as ***cardiovascular agents.***

CARDIOVASCULAR ACTIVITY

Quinoline-4-carboxylic acid derivatives were synthesized and evaluated for angiotensin II receptor antagonistic activity and found to be active hypertensive agents (Lloyd *et al*., 1994)

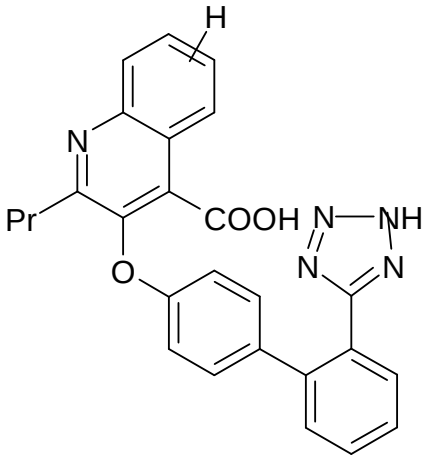


Figure 2

7-substituted or un-substituted 3-acetyl-7, 8-dihydro-2, 5(1*H*, 6*H*)-quinolinediones were synthesized and evaluated their inotropic effect (Presti*et al.,* 1999).

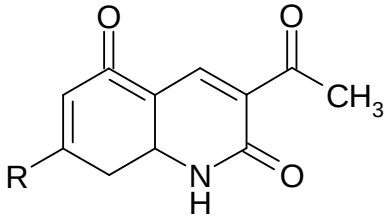


Figure 3

Table 1

S. No	-R
1	-$(CH_2)_3$
2	-$CH_2CH(CH_3)CH_3$
3	-$CH_2C(CH_3)_2CH_3$
4	-$CH_2CH(C_6H_5)CH_3$

6-cyclic aliphatic amino-7-nitro-3,4-dihydroquinoline-2(1*H*)-one derivatives were synthesized and estimated for platelet aggregation inhibitory effect, cardio tonic action and chonotropic activity and found to be selective platelet aggregation inhibitors and proved that 6-(4-ethoxycarbonylpiperidino)-7-nitro-3,4-dihydroquinoline-2(1*H*)-one was most potent and highly selective.**(**Iyobe*et al.*, 2001)

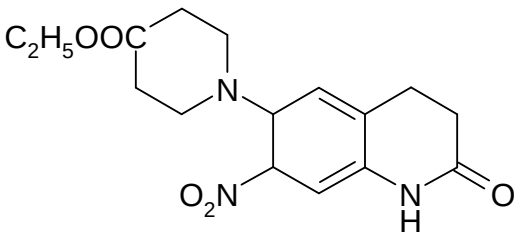


Figure 4

Aryl-fused tetrahydropyranylidene and cyclohexylideneaminoguanidine derivatives were synthesized and evaluated for their inhibitory effects on rat platelet NHEs and showed that *S* isomer of tetrahydroquinoline derivatives which contain a methyl group in the 4-position and a halogen or methyl group in the *o*-position of aryl moiety showed high inhibitory activity. Compound (5*E*,7*S*)-[[7-(5-fluoro-2-methylphenyl)-4-methyl-7,8-dihydro-5(6*H*)-uinolinylidene] amino] guanidine dimethanesulfonate (T-162559) was found to be a potent inhibitor with IC_{50} values of 14 and 13 nM, of both rat and human platelet NHEs, respectively. Compound T-162559(0.1 mg/kg, intravenously administered 5 min or 2 h before coronary occlusion) showed significant activity in a rat myocardial infarction model in vivo (1 h ischemia-24 h reperfusion) and was proved to be a potent and long-lasting protective agent against cardiac injuries induced by ischemia-reperfusion (Fukumoto*et al*.,2001).

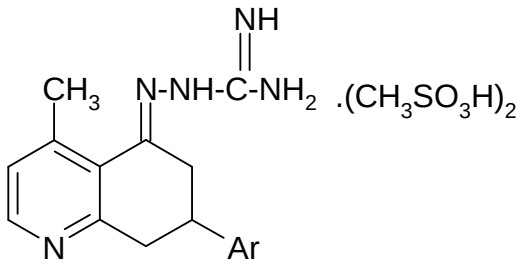


Figure 5

Ar= 5-fluoro-2-phenyl

Morizawa*et al*.,reported the trifluoromethane sulfonamide phenyl-substituted quinoline GA 0113 have been synthesized from *o*-nitrobenzoyl chloride. GA 0113 displaced specific binding of $[^{125}I]$-Sar1, Ile^8-Ang II to AT_1 receptors in membrane from Sf-9 cells. GA 0113 inhibited the Ang II-induced pressor response with ID_{50} of 0.032 mg/kg and dose-dependently increased plasma renin activity for 48 h in conscious normotensive dogs (Morizawa*et al.*, 2001).

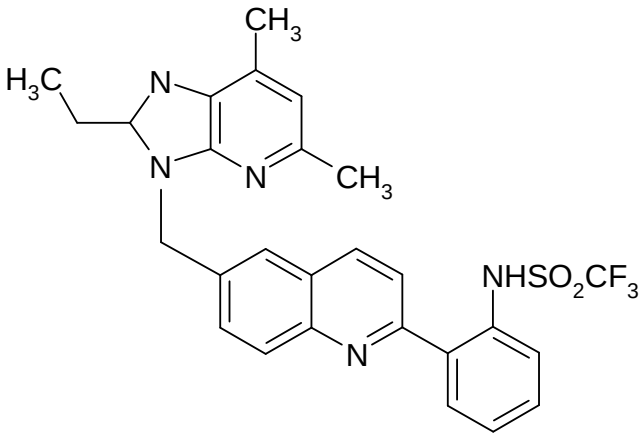


Figure 6

15 novel decahydroquinoline derivatives were synthesized and their antiarrhythmic and endothelial activity was estimated. Out of 15 compounds only four showed more activity in the model of aconitine–induced arrhythmias, to a lesser extent in calcium chloride-induced arrhythmias and no activity in adrenaline induced arrhythmias model and were found to exhibit similar activity to that of quinidine and procainamide. Also 3 and 4 were found to induce coronary vasodilation mediated by endothelium-derived NO (Kozlovski*et al*., 2004; Praliyev*et al*., 1989).

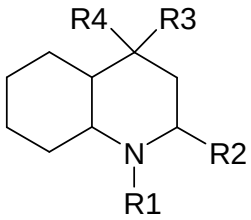
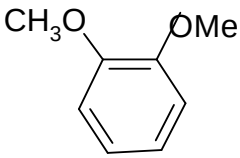
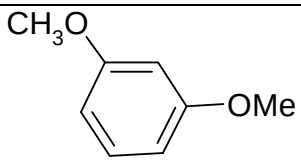


Figure 7

Table 2

S no.	-R_1	-R_2	-R_3	-R_4
1	-H		=O	
2	-H		=O	
3	$-CH_2CH_2C_6H_5$	$-CH_3$[2]	$-OCOC_6H_5$[2]	-H
4	$-CH_2CH_2C_6H_5$	$-CH_3$[2]	$-OCOC_6H_5$[1]	-H

Pandey*et al*., reported 1, 3, 5-tris-(8-aralkyl amido/imido-alkyl-7-hydroxy-4-methyl-2-oxo-quinolinyl)-2, 4, 6-hexahydro-s-triazines (**A-C**) and tested their antiviral activity upon *Japanese encephalitis virus (JEV)* and *Herpes simplex virus-1*(HSV-1) and antihypertensive activity. (Pandey*et al.*, 2004)

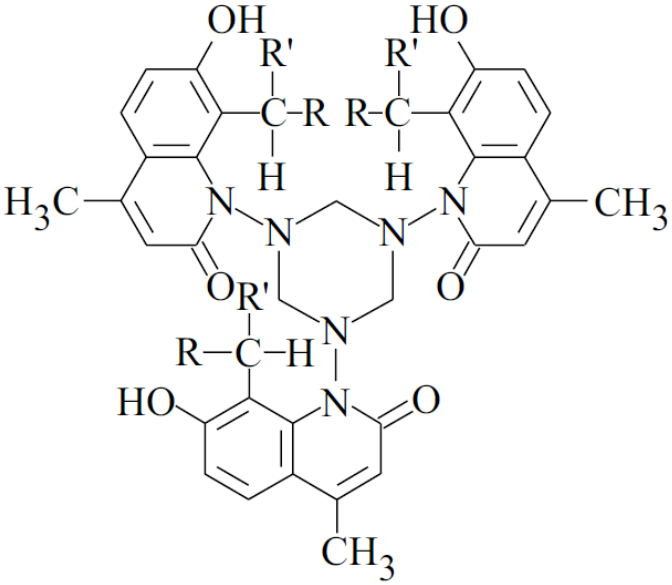


Figure 8

Table 3

S. No.	-R	-R'
A	-o-OH-C_6H_4	-Salicylamido
B	-H	-Phthalamido
C	--H	-Salicylamido

A series of unsymmetrical alkyl, cyclo-alkyl and aryl ester analogues of 2-methyl-4-(1-methyl)-5-nitro-2-imidazolyl-5-oxo-1,4,5,6,7, 8-hexahydroquinolin-3-arboxylate, third-generation 1,4-dihydropyridine drugs were synthesized which possess cardio-selective Ca2+-channel agonist ⁄ vascular selective smooth muscle Ca2+ channel antagonist property and were found to be effective in treatment of congestive heart failure (CHF) (Miri*et al.*,2007).

Cai*et al*., reported novel 4-thiophenyl quinoline-based mevalonolactone derivatives from ethyl 6,7,8-trisubstituted-4-chloro-quinoline-3-carboxylates and tested their potential to inhibit the rat HMG CoA reeducate in vitro and found that (4*R*,6*S*)-6-[(*E*)-2-(6,7,8-trifluoro-4-isopropylthio-phenyl-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**1**) and (4*R*, 6*S*)-6-[(*E*)-2-(6-fluoro-4,7-di-(3-methoxy-thiophenyl)-quinoline-3-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**2**) were approximately three times more potent than rosuvastatin or pitavastatinin inhibiting HMG CoA reeducate.

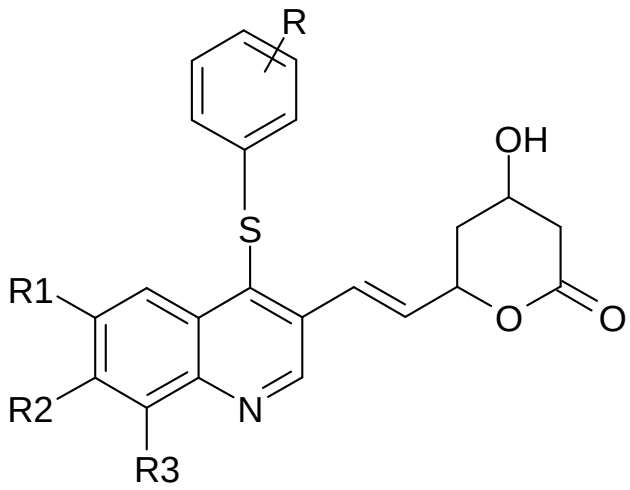


Figure 9

Table 4

S No	$-R_1$	$-R_2$	$-R_3$	-R
1	4-$CH(CH_3)_2$	-F	-F	-F
2	3-OCH_3	-F	SC_6H_4-3-OCH_3	-H

A few phenyl acetic acid based quinolines were developed which act as agonists at liver X receptors. These agents have good binding affinity for LXRb and LXRa receptors and found to be active atherosclerotic agents (Hu *et al*., 2007).

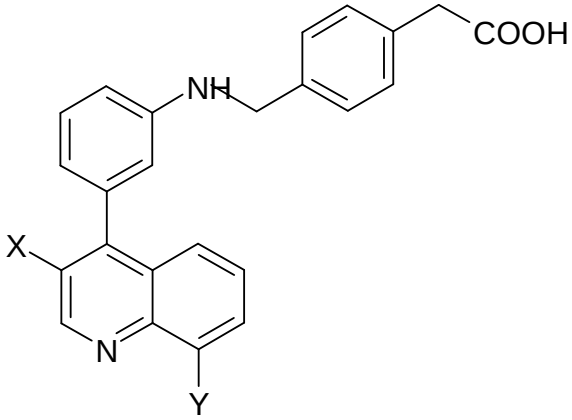


Figure 10

X = -CH_2Ph, -COPh, -CN, -$CONH_2$ **Y** = -CF_3, -CH_3, -Cl

Ramos *et al*. synthesized tetrahydroquinolinamines and estimated for their platelet aggregation inhibition activity and found to be potent inhibitors of platelet aggregation (Ramos *et al*., 2008).

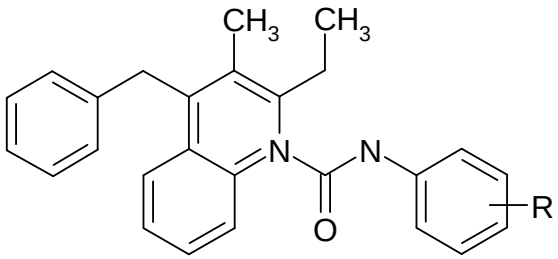


Figure 11

R = 3-Cl, 3-Br, 3-OCH_3

Derivatives of in dole, quinoline and purine with an attached nitrate ester group were designed and synthesized and found that the in dole and quinoline derivatives 4 and 5 showed K^+ATP channel opening property while Purine analogues, substituted at the position 6 by a piper dine moiety and at position 9 by an alkyl nitrate showed combined effects of the nitrate containing K^+-ATP channel openers and those of adenosine. Compounds below reduced infarction and malondialdehyde (MDA) level at reperfusion in anesthetized rabbits raised c GMP and MDA during ischemia (Fotopoulou*et al*., 2008).

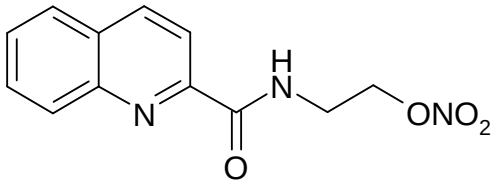


Figure 12

Novel highly selective pyrroloquinoxaline 5-HT3 receptor (5-HT3R) modulators were reported and tested their vivo biological activity by interacting them directly with myocardial 5-HT3Rs. A and B showed chemotropic modulation (right atrium) but not inotropic modulation(left atrium) at the cardiac level, being antagonist and partial agonist, also both

these modulators were found to have poor blood-brain barrier permeability and hence showed cardiac pharmacological activity only(Morelli*et al.*,2008).

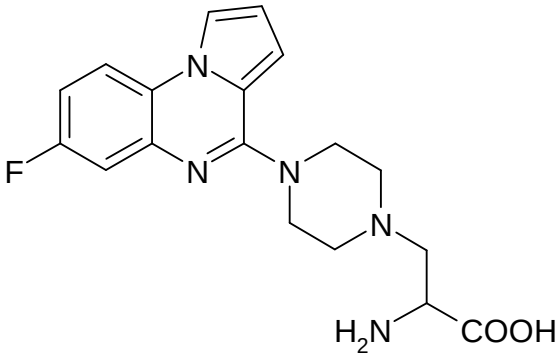


Figure 13

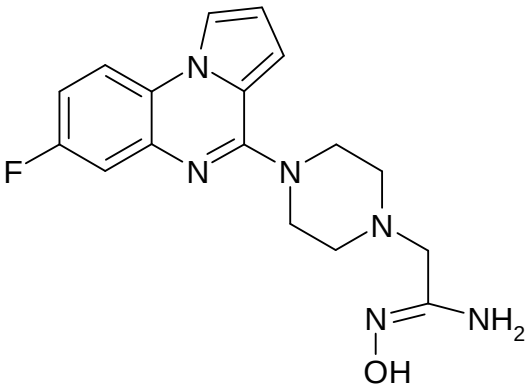


Figure 14

Certain bi-aryl-ether amide quinolines were synthesized and evaluated for liver X receptor agonistic activity and found to be useful in conditions of dyslipidaemia and are also used to reverse the conditions of arteriosclerosis (Bernotas*et al*., 2009).

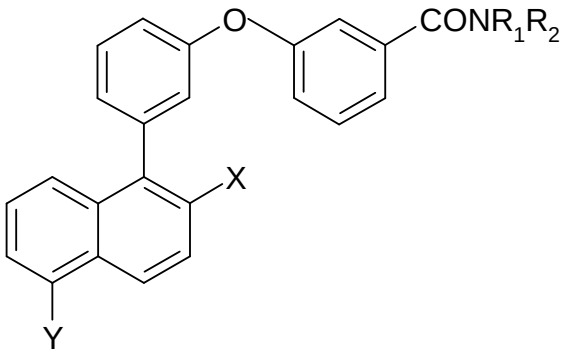


Figure 15

X = -CF_3, Cl, **Y** = -CH_2Ph

R_1, R_2 = -Methyl ester, -Pyrrolidine, Piper dine, Morph line

Sadeghian*et al*., designed and synthesized thirteen PDE-3 inhibitors (4-[(4-methyl-2-oxo-1, 2-dihydro-6-quinolinyl) oxy] butanamide analogs and reported their synthesis and cardio tonic activity using the spontaneously beating atria model for their contractile and chronoscopic activity and showed that selective PDE-3 inhibitors corrects the cardiac contractility and may be used in congestive heart failure but these agents showed pro-arrhythmic side effects. Compound 6-(4-(4-methylpiperazin-1-yl)-4-oxobutoxy)-4-methylquinolin-2(1H)-one (Sadeghian*et al*., 2009)

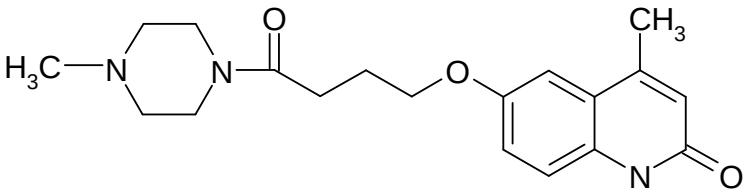


Figure 16

Mao *et al*., reported many substituted (quinolinecarbonyl)guanidine derivatives and tested their activity as NHE inhibitors that are used to inhibit the Na^+/H^+exchanger (NHE) which is a protein expressed in many mammalian cell types and is involved in intracellular pH (pHi) homeostasis by exchanging extracellular Na^+ for intracellular H^+. Amongst nine isoforms NHE-1 is the most predominant isoform expressed in mammalian cardiac muscle and most compounds can inhibit NHE-1mediated platelet swelling in a concentration-dependent manner and compound below was found to be the most active and more potent than cariporide and also possesses the in vivo cardio protective effects against SD rat myocardial ischemic-reperfusion injury superior (Mao *et al.*, 2009).

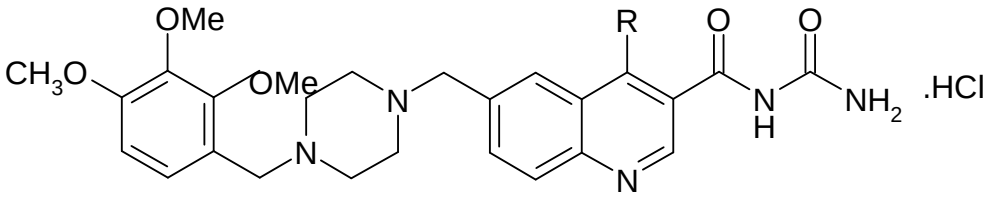


Figure 17

R = 4-EtO -C_6H_4-NH-

Liu *et al*., synthesized a series of 1-substituted-N-(4,5-dihydro-1-methyl-[1,2,4]triazolo[4,3-a]quinolin-7-yl) piperidine-4-carboxamides and tested their positive inotropic activity against standard drug milrinone in isolated rabbit-heart preparations by measuring left atrium stroke volume and found that 1-(2-fluorobenzyl)-N-(4,5-dihydro-1-methyl-[1,2,4]triazolo[4,3-a]quinolin-7-l)piperidine-4-carboxamide ( ) was the most potent(Liu *et al*., 2009).

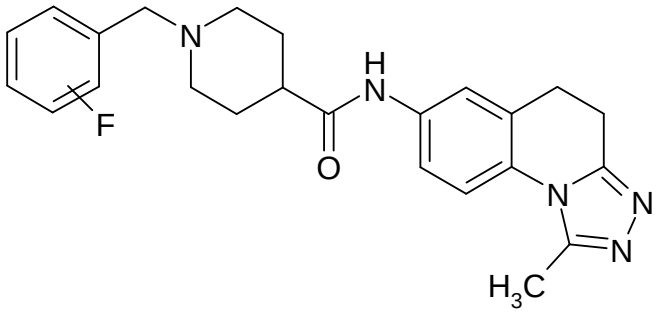


Figure 18

Nikpour*et al*., reported ten synthetic compounds (3-[(4-methyl-2-oxo-1, 2-dihydro-6-quinolinyl)oxy]methyl, benzamide analogs based on the structure of vesnarinone and evaluate their inhibitory activity against human PDE-3A and PDE-3B and found that these compounds showed better chonotropic and contractile activity than vesnarinone and compound 4-Methyl-6-({3-[(4-ethylpiperazino)carbonyl]-benzyl}oxy)-1, 2-dihydro-2-quinolinone showed selectivity for increasing the force of contraction than the rate of frequency (Nikpour*et al*., 2009).

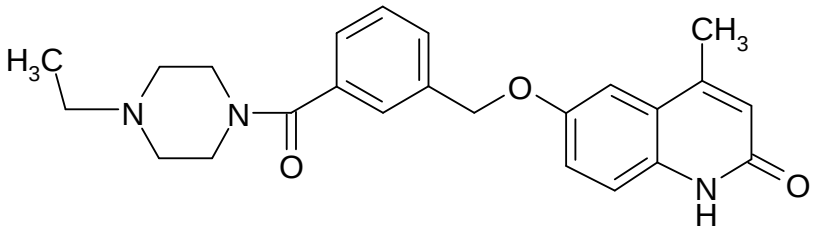


Figure 19

A series of 4-phenoxy quinoline based mevalonolactone derivatives were synthesized and tested for 3 hydroxy-3-methyl glutaryl CoA reeducate (HMG CoA reeducate) inhibiting activity. Compound (4R,6S)6{(E)-2-[6 fluoro-7-chloro-4-(4-fluorophenoxyquinoline)-3-yl]ethenyl}3,4,5,6tetrahydro-4-hydroxy-2-Hpyran-2-one , possess more potent activity than rosuvastatin or pitavastatin to inhibit the rat HMG CoA reeducate in vitro and was selected for the extensive preclinical development as a potential hypocholesterolemic candidate (Cai*et al.*,2010).

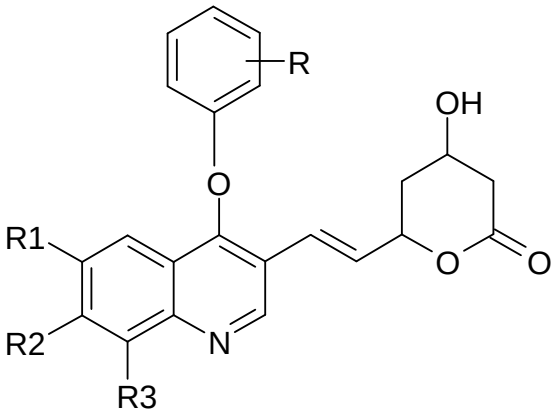


Figure 20

Table 5

S no.	-R_1	-R_2	-R_3	-R
1	-F	-Cl	-H	-F

Recently7-alkoxy-4,5-dihydro-[1,2,4]oxadiazolo[4,3-a]quinolin-1-ones designed and synthesized and tested for their negative inotropic activity in isolated rabbit heart preparations by measuring the left atrium stroke volume and found that all compounds minimize the cardiac workload by decreasing heart rate and contractility (inotropic effects) and compound 7-(3-Chlorobenzyloxy)-4,5-dihydro-[1,2,4]oxadiazolo[4,3-a]quinolin-1-one was most potent amongst them (Hong *et al*., 2011)

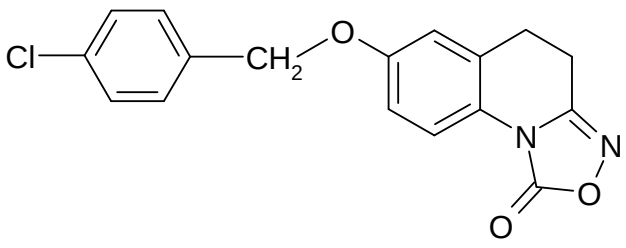


Figure 21

Wu*et al*., reported two series of N-(1-oxo-1,2,4,5-tetrahydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)acetamides bearing piperazine and 1,4-diazepane derivatives and tested their positive inotropic activity on isolated rabbit heart preparations by measuring left atrium stroke volume and found that most of the derivatives showed better in vitro positive inotropic activity than milrinone. They proved that 2-(4-(4-chlorobenzyl)-1,4-diazepan-1-yl)-N-(1-oxo-1,2,4,5-tetrahydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)acetamide was the most potent and also checked the chronoscopic effects of the compounds that exhibited inotropic effects (Wu*et al*., 2012).

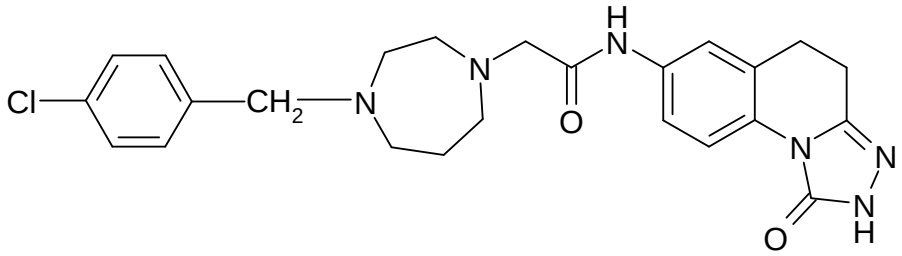


Figure 22

A series of (E)-2-(4-cinnamylpiperazin-1-yl)-N-(1-substituted-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)acetamides were reported and tested for their positive isotropic activity and chemotropic effect on isolated rabbit heart preparations by measuring the left atrium stroke volume. Compound N-(1-(3- chlorophenyl)-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)-2-(4-cinnamylpiperazin-1-yl)acetamide was found to be the most potent when compared with standard drug milrinone(Wu*et al*., 2012).

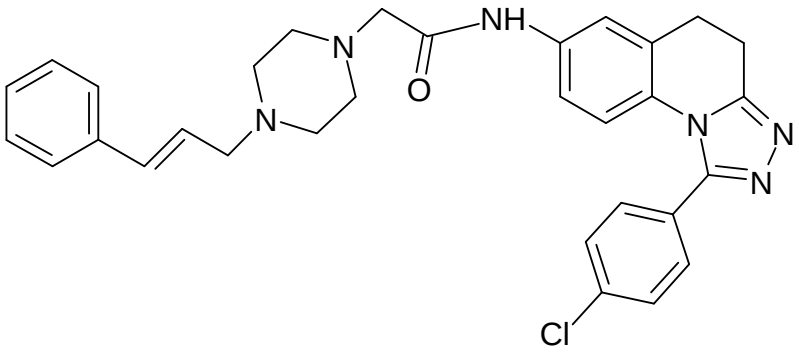


Figure 23

ACKNOWLEDGEMENTS

Authors are thankful to Principal of Khalsa College of Pharmacy and IELTS academy, Amritsar for their support and providing facilities for this work.

REFERENCES

1. Ceconi C, Cargnoni A, Pasini E, Condorelli E, Curello S, Ferrari R. Evaluation of phospholipids per oxidation as malondialdehyde during myocardial ischemia and reperfusion injury. Am J Physiol 1991; 260:H1057–H1061.
2. Dhalla NS, Panagia V, Singal PK, Makino N, Dixon IM, EyolfsonDA. Alterations in heart membrane calcium transport during the development of ischemia–reperfusion injury. J Mol Cell Cardiol 1988; 20(Suppl 2):3–13.
3. DhallaNS, Wang X, Beamish RE. Intracellular calcium handling in normal and failing hearts. ExpClinCardiol

1996; 1:7–20.

4. Dixon IM, Eyolfson DA, Dhalla NS. Sarcolemmal Na –Ca exchange activity in hearts subjected to hypoxia reoxygenation. Am J Physiol 1987; 253:H1026–H1034.
5. Ferrari R, Ceconi C, Curello S et al. Oxygen-mediated myocardial damage during ischemia and reperfusion: role of the cellular defenses against oxygen toxicity. J Mol Cell Cardiol 1985;17:937–945
6. Ferrari R. The role of mitochondria in ischemic heart disease. J CardiovascPharmacol 1996; 28(suppl 1):S1–10.
7. Fotopoulou et al. Design and synthesis of nitrate esters of aromatic heterocyclic compounds as pharmacological preconditioning Laboratory of Molecular Pharmacology, Department of Pharmacy, University of Patras, 2008;
8. Fukumoto et al. Novel, Non-acylguanidine-type Na+/H+ Exchanger Inhibitors: Synthesis and Pharmacology of 5-Tetrahydroquinolinylidene Aminoguanidine Derivatives Pharmaceutical Research Division, 2001;
9. Garlick PB, Davies MJ, Hearse DJ, Slater TF. Direct detection ofree radicals in the reperfused rat heart using electron spin resonance spectroscopy. Circ Res 1987; 61:757–760.
10. Grech ED, Dodd NJ, Jackson MJ, Morrison WL, Faragher EB, Ramsdale DR. Evidence for free radical generation after primary percutaneous transluminal coronary angioplasty recanalization in acute myocardial infarction. Am J Cardiol 1996; 77: 122–127?
11. Griendling KK, Alexander RW. Oxidative stress and cardiovascular disease. Circulation 1997; 96:3264–3265.
12. Hong et al. Synthesis and negative inotropic effects evaluation of 7-substituted-4,5-dihydro-[1,2,4]oxadiazolo[4,3-a]quinolin-1-ones,2013;
13. Iyobe et al Studies on New Platelet Aggregation Inhibitors 1. Synthesis of 7-Nitro-3,4-dihydroquinoline-2(1*H*)-one Derivatives *Central Research Laboratories, Kissei Pharmaceutical,* 2001
14. Kaplan P, Lehotsky J, Racay P. Role of sarcoplasmic reticulum in the contractile dysfunction during myocardial ischaemia and re- perfusion. Physiol Res 1997; 46:333–339.
15. Kato K, Shao Q, Elimban V, Lukas A, Dhalla NS. Mechanism of depression in cardiac sarcolemmal Na –K ATPase by hypochlorous acid. Am J Physiol 1998; 275:C826–C831.
16. Kozlovski ET al.Antiarrhythmic Profile and Endothelial Action of Novel Decahydroquinoline Derivatives Praliyev KD, Fishchuk EV, Malchikova LS: Synthesis and cardiotropic activity of new derivatives of two stereoisomers of 1–[2-(3, 4-dimethoxyphenyl-ethyl)]-2-methyl-4-ethynyl-4-oxy-Trans-decahydroquinoline. Chem Pharm J, 1989, 8, 939–941.
17. Kusumoto et al.In vitro and in vivo pharmacology of a structurally novel Na+-H+ exchange inhibitor, T-162559*,British Journal of Pharmacology (2002) 135, 1995 ± 2003;
18. Liu et al, Synthesis and inotropic evaluation of 1-substituted-N-(4,5-dihydro-1-methyl-[1,2,4]triazolo[4,3-a]quinolin-7-yl)piperidine-4-carboxamides Laboratory of Natural Resources and Functional Molecule. 2009;
19. Mao et al.Synthesis and Naþ/Hþ Exchanger-1 Inhibitory Activity of Substituted (Quinolinecarbonyl) guanidine Derivative. Department of Medicinal Chemistry, 20009;

20. Miri, R. Javidnia, K. Mirkhani,H, Hemmateeneja, B, Sepeher Z, Zalpour M,, et al. Synthesis, QSAR and Calcium Channel Modulator Activity of New Hexahydroquinoline Derivatives Containing Nitroimidazol, Medicinal& Natural Products Chemistry Research Centre, Shiraz University of Medical Sciences, 2007;

21. Mitsos SE, Fantone JC, Gallagher KP et al. Canine myocardial reperfusion injury: protection by a free radical scavenger, *N*-2- mercaptopropionyl glycine. J CardiovascPharmacol 1986; 8:978–988.

22. Morellietal. Specific Targeting of Peripheral Serotonin 5-HT3 Receptors. Synthesis, Biological Investigation, and Structure-Activity Relationships J. Med. Chem. 2009, 52, 3548–3562

23. Musat S, Dhalla NS. Alteration in cardiac sarcolemmal ATP receptors by oxyradicals. Ann NY AcadSci 1996;793:1–12

24. Pandey et al. Synthesis and biological activity ofsubstituted 2,4,6-s-triazines Chemistry Department University of Lucknow, 2004;

25. Presti et al. 3-Acetyl-5-acylpyridin-2(1*H*)-ones and 3-acetyl-7,8-dihydro-2,5(1*H*,6*H*)-quinolinediones: synthesis, cardiotonic activity and computational studiesVolume 54, Issue 7, 30 July 1999, Pages 465–474;

26. Sadeghian et al. Design, synthesis and biological evaluation of6-(benzyloxy)-4-methylquinolin-2(1H)-one derivatives as PDE3 inhibitors.2009. Department of Chemistry, School of Sciences, Islamic Azad University, Ahvaz Branch, Ahvaz, 61349-68875,

27. Slezak J, Tribulova N, Pristacova J et al. Hydrogen peroxide changes in ischemic and reperfused heart. Cytochemistryandbiochemical and X-ray microanalysis. Am J Pathol 1995;147:772–

28. Suzuki S, Kaneko M, Chapman DC, Dhalla NS. Alterations in cardiac contractile proteins due to oxygen free radicals. BiochimBiophysActa 1997;1074:95–100

29. Wu et al. Synthesis and positive isotropic evaluation of Evaluation of (E)-2-(4-Cinnamylpiperazin-1-yl)-N-(1-substituted-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)acetamidesmoieties Laboratory of Natural Resources and Functional Molecules of the changbai Mountain, Arch. Pharm. Chem. Life Sci. 2012, 000, 1–9

30. Wu et al. Synthesis and positive inotropic evaluation of N-(1-oxo-1,2,4,5-tetrahydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)acetamides bearing piperazine and 1,4-diazepane moieties Laboratory of Natural Resources and Functional Molecules of the Changbai Mountain, Arch. Pharm. Chem. Life Sci. 2012, 000, 1–9

31. Wua, Y et al. Synthesis and positive inotropic evaluation of N-(1-oxo-1,2,4,5-tetrahydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)acetamides bearing piperazine and 1,4-diazepane moieties a Key Laboratory of Natural Resources and Functional Molecules of the Changbai Mountain, 2012;