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Molecular Docking Studies of novel Quinazoline-2-imine derivatives as Potential Anti-inflammatory Agents Against TGF Beta Receptor Type 1

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Abstract

Quinazoline hetero cyclic compounds found to possess various pharmacological activities like anti-cancer, anti-inflammation, anti-bacterial, analgesia, anti-virus, anti-cytotoxin, anti-spasm, anti-tuberculosis, anti-oxidation, anti-malarial, anti-hypertension, anti-obesity, anti-psychotic, anti-diabetes, etc. In this study, few novel quinazolinone-2-imines were prepared from substituted chalcones. These chalcones were prepared by condensation of cyclohexanone with various substituted aromatic aldehydes (Claisen-Schmidt condensation reaction-CSCR). Quinazolinone-2-imines were characterized by its melting point, Fourier transform infrared spectroscopy (FTIR), Nuclear magnetic resonance (^{1}HNMR) and mass spectroscopy and CHNO analysis. These molecules screened for *in-vitro* anti-inflammatory activity by the gelatin zymography technique, the results obtained for inflammation were well supported by molecular properties, pharmacological and docking score by *in-silico* methods like Prediction of Activity Spectra for Substances (PASS), Molinspiration and docking studies against TGF beta receptor type 1respectively. The *in-silico* methods are more helpful in drug discovery and development. Based on all these results, the synthesized newer quinazolinone-2-imines were proven for their potent anti-inflammatory activity.

Keywords: Quinazoline-2-imine, Chalcones, Anti-inflammatory activity, Molecular docking.

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1. Introduction

Quinazolines are the compounds with heterocyclic fused ring, they have considerable interest because of the diverse range of their pharmacological activities [1-5]. Mainly the substituted quinazolines has a wide range of activities in the literature survey like anti-cancer, anti-inflammatory, anti-bacterial, anti-hypertension, analgesia, anti-viral, anti-cytotoxic, anti-spasmodic, anti-tubercular, anti-oxidant, anti-malarial, diuretic, anti-obesity, anti-psychotic, anti-diabetic and many other biological activities [6-10]. These Quinazoline pharmacophore is also widely used in preparation of various synthetic compounds by substituting with various functional groups and aromatic compounds as a drug molecule.

α,β- unsaturated carbonyl compounds are also known as chalcones. These are widely distributed in nature in the form of flavonoids. Chalcones can be synthesized by CSCR [11-15], hence, chalcones are being convenient to modify and react with functional groups to give a variety of compounds. The present research was aimed to synthesize biologically potent newer quinazolines. Here, they were synthesized by two steps, in step-1 formation of chalcones and step-2 formation of quinazolines from chalcones [16-18]. The synthesized compounds were characterized by structural data like FTIR, ^{1}HNMR, MASS spectroscopy and CHNO analysis. The synthesized compounds were predicted for their biological activity by using *in-silico* method-PASS online software and molecular properties are calculated by Molinspiration [19].

Based on those predictions, the synthesized compounds were screened for anti-inflammatory activity (gelatin zymography method) by the detection of NMT-2 and NMT-9 using tetracycline hydro chloride as positive control and tonsil sample as negative control. Molecular properties, drug likeness properties and toxic properties were predicted to show its better qualities as compared with the existing quinazolines. The docking studies were further proven the efficiency of these quinazolinone-2-imines as a potent anti-inflammatory agent as compared with the standard drug tetracycline.

2. Experimental

2.1. Materials and equipment

Melting point of the synthesized compounds was determined in open capillary tube using digital melting point apparatus, expressed in Celsius and is uncorrected. FTIR spectra were recorded on a Shimadzu FTIR-4000 (Japan) by KBr disk method. Mass spectra were obtained on JEOL GC mate-II GC-Mass spectrometer (USA) at 70ev by direct insertion probe method. ^{1}HNMR spectra were taken on Bruker AV400-400 MHZ high resolution multi nuclear FT-NMR spectrometer (USA) and Chemical shifts were expressed in d (ppm) relative to TMS as an internal standard using DMSO-d6 as solvent. The purity of the compounds was checked on silica gel-coated aluminum sheets (Merck, 1.005554, silica gel HF254–361, Type 60, 0.25 mm, Darmstadt, Germany) by thin-layer chromatography (TLC). TLC was performed on silica gel G for TLC (Merck, India) and spots were visualized by iodine vapor or by irradiation with ultraviolet light (short wave length, 254 nm).

2.2. Method

New synthetic approach for development of series of quinazolinone-2-imine derivatives were shown in figure 1.

Step-I: Ethanol about 50 ml was added to a mixture of 0.01 M cyclohexanone and 0.01 M aromatic aldehyde (p-dimethyl amino benzaldehyde, Anisaldehyde, p-chloro benzaldehyde, Benzaldehyd, Vanillin, 4-nitrobenzaldehyde, Ethyl vanillin, 3,4-

dichloro benzaldehyde, p-toluraldehyde and salicylaldehyde), cooled to 5-10°C. To this mixture, 5 ml of aqueous NaOH (70%) was added drop wise with constant stirring. The reaction mixture was further stirred for 2-3 h, left over night and neutralized with concentrated HCl. The obtained product was filtered, recrystallized and used for further studies i.e. step-II.

Step-II: The product formed in Step-I was mixed with guanidine (0.1 mole) and 2-3 drops of pyridine was added. Ethanol about 50 ml was added to the above mixture as a solvent and refluxed for 6 h at 60ºC. The solvent was distilled off and the product was poured into crushed ice. The resultant product was then recrystallized from ethanol.

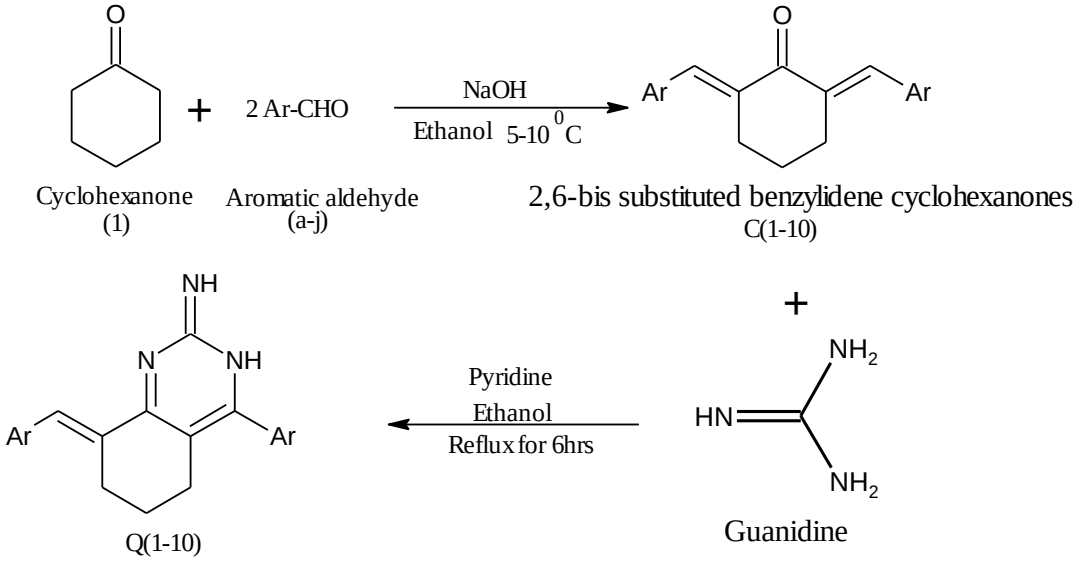


Figure 1. Scheme of the work.

3. Results and discussion

3.1. Characterization

3.1.1. *4-(8-(4-(dimethylamino)benzylidene)-2-imino-2,3,5,6,7,8-hexahydroquinazolin-4-yl)-N,N-dimethylbenzenamine (Q1)*

Compound (Q_1) analyzed for $C_{25}H_{29}N_5$, the yield was found to be 80.5% and melting point range was found to be 130-135°C. The FTIR (cm^{-1}) spectrum (Figure 2) showed the characteristic bands at 851.60 (C-N stretching), 2848.96 (N-CH_3 stretching), 1539.06 (C=N stretching), 1571.46 (N-H deformation), 1152.77 (C-C stretching), 752.761 (C=C stretching) and 2922.92 (-CH_3 stretching). The ^{1}HNMR spectrum (Figure 2) of compound Q1 showed the characteristic peaks at 6.758-7.317 (m, 8H, Aromatic), 2.511 (s, 3H, -CH_3), 6.820 (s, 1H, -CH-), 1.732-1.804 (m, 6H, -CH_2) and 2.300-2.385 (2H, -NH). It was observed from the mass spectrum that the molecular ion peak was found at m/z 399.2 (Figure 2). CHNO analysis was found to be C-75.15, H-7.32 and N-17.53.

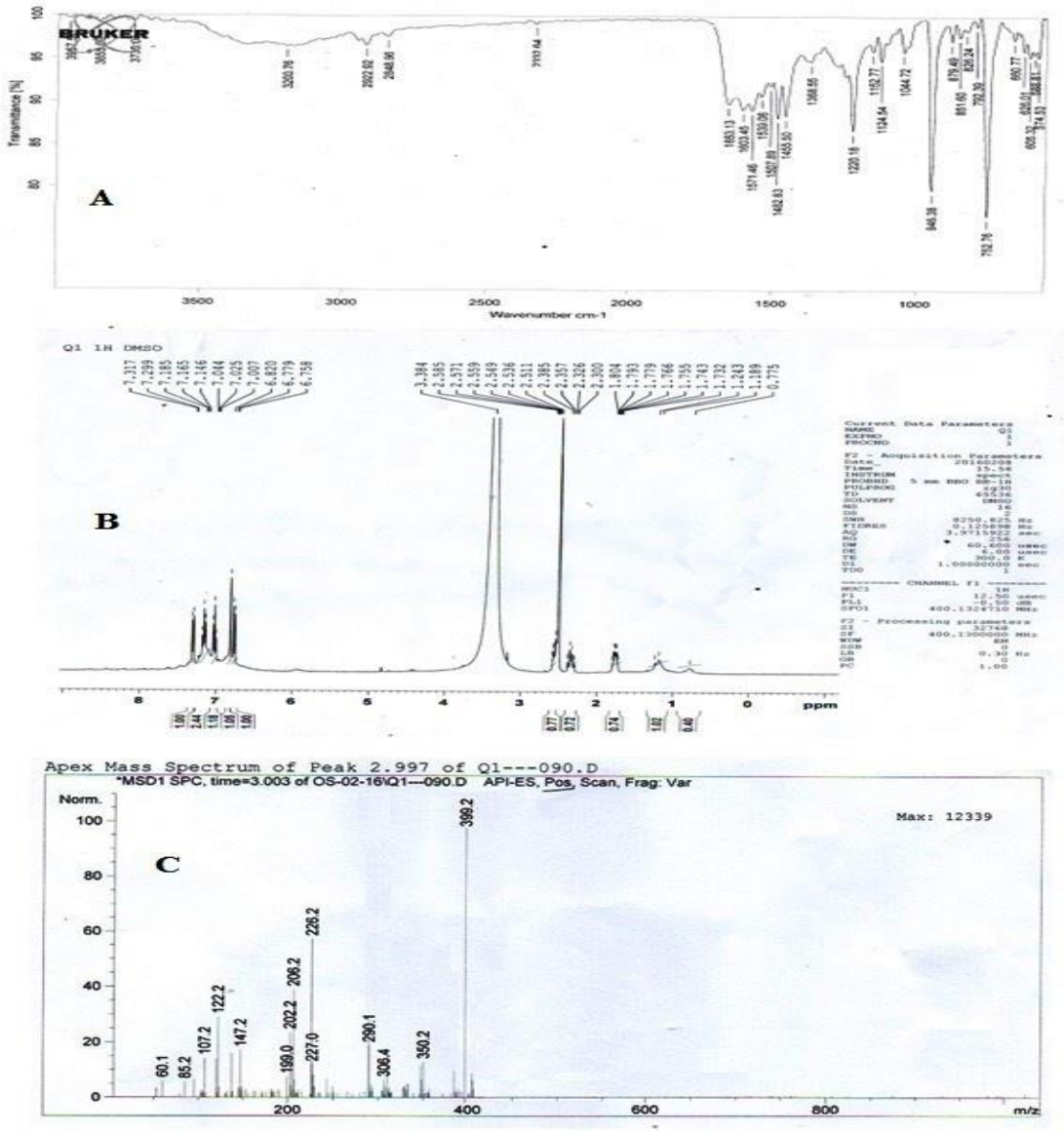


Figure 2. Compound Q1 analysis: A. FTIR Spectra, B. ^{1}H NMR Spectra, C. Mass Spectra of compound Q1.

3.1.2. *8-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinazolin-2(3H)-imine (Q2)*

Compound (Q2) analyzed for $C_{23}H_{23}N_3O_2$, the yield was found to be 82.5% and melting point range was found to be 160-165°C. The FTIR (cm^{-1}) spectrum (Figure 3) showed the characteristic bands at 2917.72 (C=C stretching), 2849.45 (C-C stretching), 1134.63 (C-O stretching), 1019.14 (C-N stretching) and 1520.40 (C=N stretching). The ^{1}H NMR spectrum (Figure 3) of compound Q2 showed characteristic peaks between 6.926-6.947 (d, 2H, Aromatic), 7.444-7.465 (d, 2H, Aromatic), 3.847 (s, 3H, $-CH_3$), 6.430 (s, 1H, -CH-), 1.772-1.837 (m, 6H, $-CH_2$) and 2.922 (2H, -NH). Molecular ion peak was observed at m/z 374.2 in its mass spectrum (Figure 3). CHNO analysis was found to be C-73.97, H-6.21, N-11.25 and O-8.50.

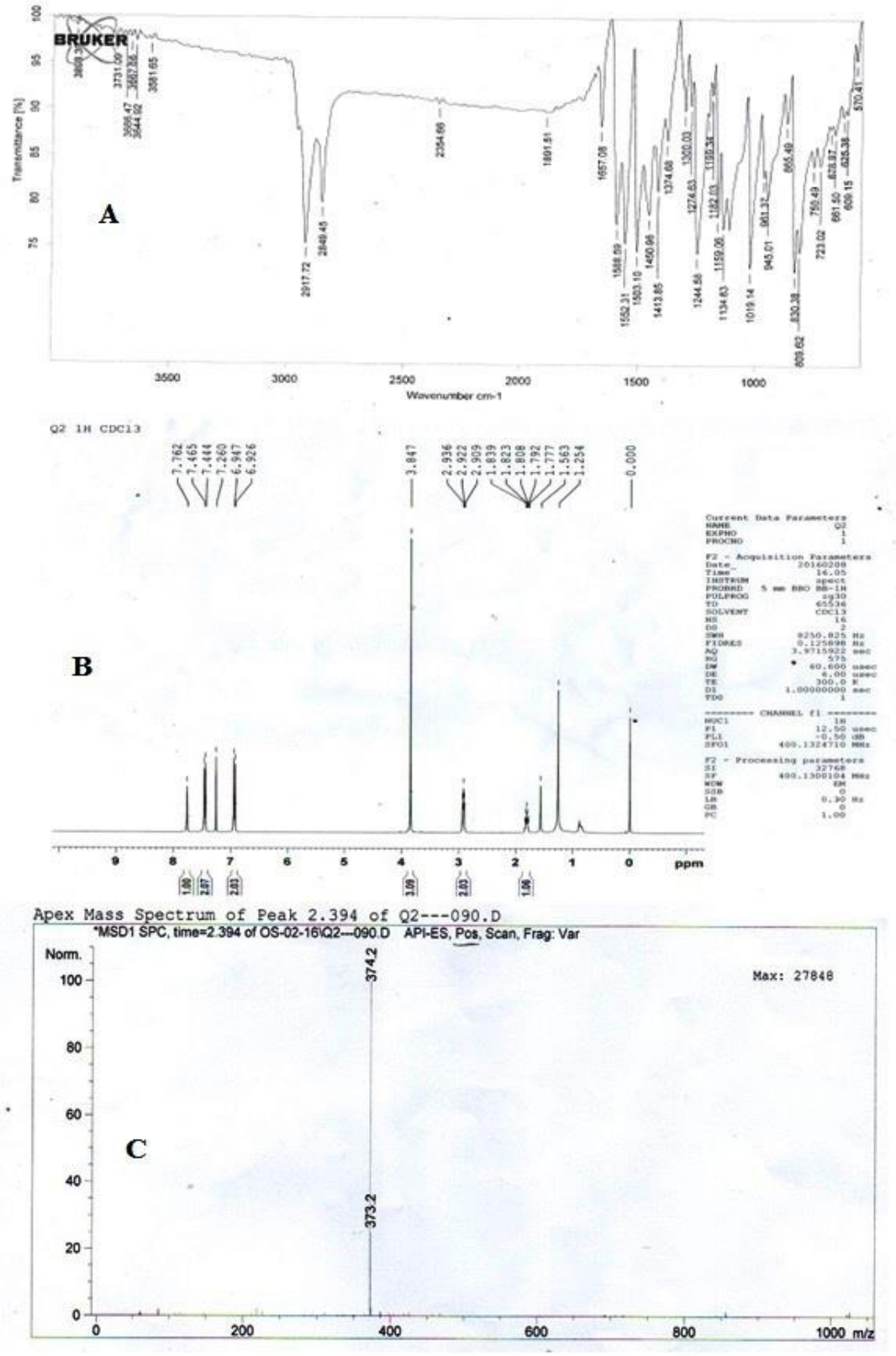


Figure 3. Compound Q2 analysis: A. FTIR Spectra, B. ^{1}H NMR Spectra, C. Mass Spectra of compound Q2.

3.1.3. *8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-5,6,7,8-tetrahydroquinazolin-2-imine (Q3)*

Compound (Q3) analyzed for $C_{21}H_{17}Cl_2N_3$, the yield was found to be 79.8% and melting point range was found to be 160-165°C. The FTIR (cm^{-1}) spectrum (Figure 4) showed the characteristic bands at 2848.75 (C-C stretching), 2065.66 (C=C stretching), 748.12 (C-Cl stretching), 3230.05 (C=N stretching), 2338.27 (N-H stretching) and 1430.65 (C-N stretching). The ^{1}HNMR spectrum (Figure 4) of compound Q3 showed characteristic peaks at 7.014-7.144 (m, 8H, Aromatic), 6.436 (s, 1H, -CH-), 1.794-1.822 (m, 6H, -CH_2) and 2.506-2.519 (2H, -NH). Molecular ion peak was found at m/z 381.2 in its mass spectrum (Figure 4). CHNO analysis is found to be C-65.98, H-4.48 and N-10.99.

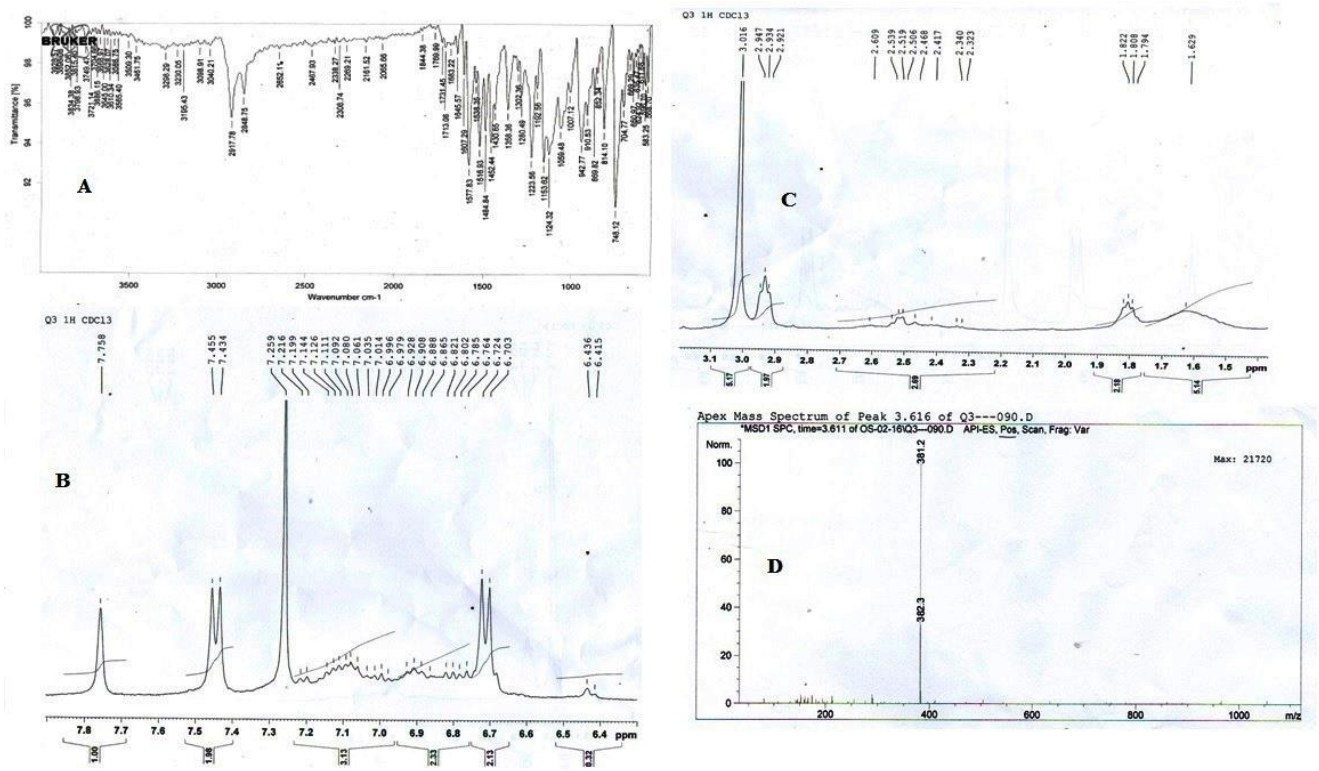


Figure 4. Compound Q3 analysis: A. FTIR Spectra, B,C ^{1}H NMR Spectra, D. Mass Spectra of compound Q3.

3.1.4. *8-benzylidene-4-phenyl-5,6,7,8-tetrahydroquinazolin-2-imine(Q4)*

Compound (Q4) analyzed for $C_{29}H_{19}N_3$, the yield was found to be 77.8% and melting point range was found to be 150-154°C. The FTIR (cm^{-1}) spectrum (Figure 5) showed the characteristic bands at 2919.36 (C=C stretching), 1581.16 (C=N stretching), 2849.37 (C-C stretching), 1313.71 (C-N stretching), 965.86 (C-H stretching) and 2353.83 (N-H stretching). The ^{1}HNMR spectrum (Figure 5) of compound Q4 showed characteristic peaks between 7.301-7.479 (m, 8H, Aromatic), 6.436 (s, 1H, -CH-), 1.255-1.766 (m, 6H, -CH_2), 1.828 (2H, -NH). Molecular ion peak was observed at m/z 313.3in its mass spectrum (Figure 5). CHNO analysis is found to be C-80.48, H-6.11 and N-13.41.

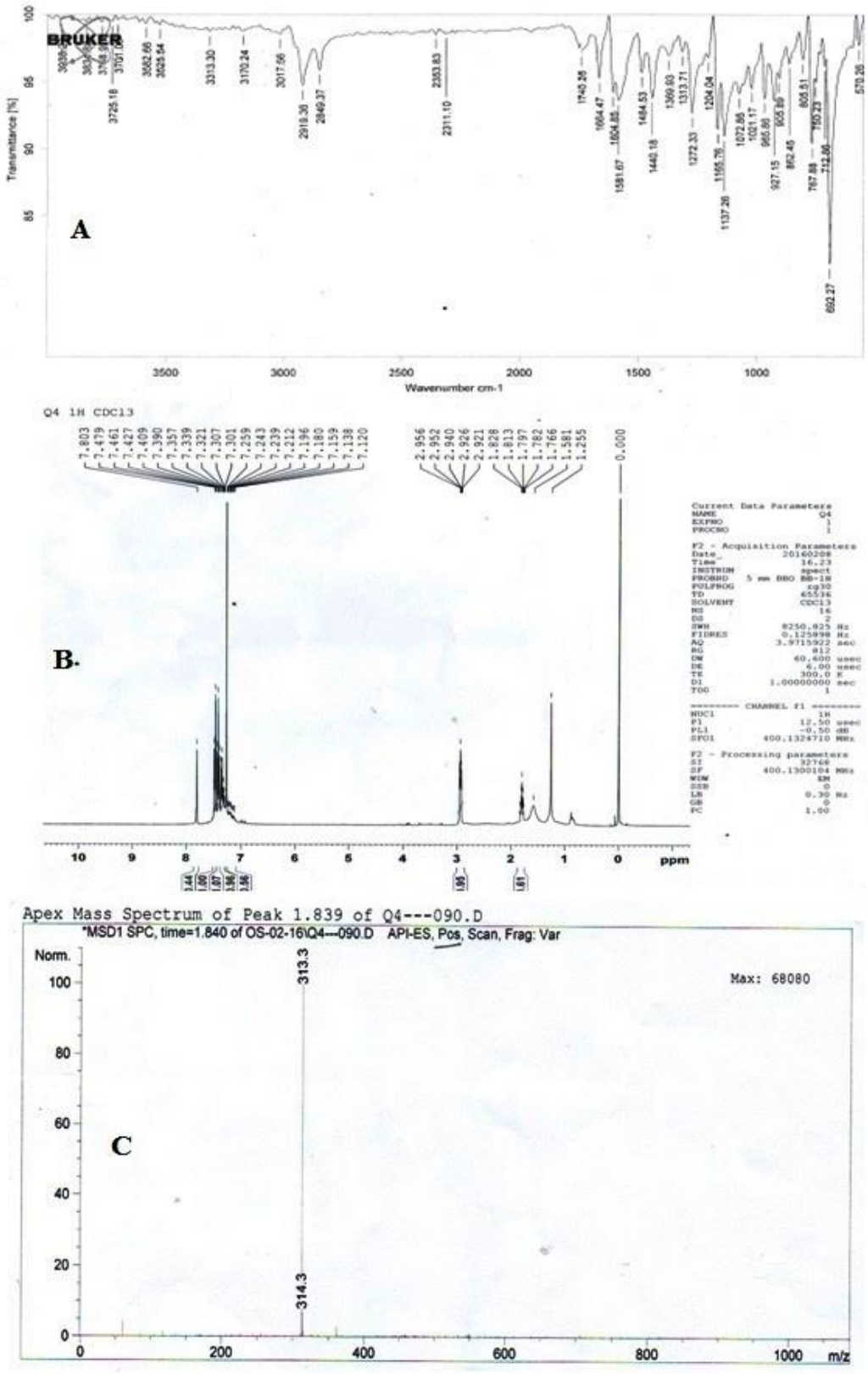


Figure 5. Compound Q4 analysis: A. FTIR Spectra, B. ^{1}H NMR Spectra, C. Mass Spectra of compound Q4.

3.1.5. *3-((4-(2-hydroxylphenyl)-2-imino-2,3,6,7-tetrahydroquinazolin-8-ylidene)methyl)phenol (Q5)*

Compound (Q5) analyzed for $C_{23}H_{23}N_3O_4$, the yield was found to be 83.5% and melting point range was found to be 175-180°C. The FTIR (cm^{-1}) spectrum (Figure 6) showed the characteristic bands at 3253.38(C-OH stretching), 2849.45(C-C stretching), 1332.70 (C-N stretching), 1539.36 (C=N stretching) and 961.36 (C=C stretching). The ^{1}HNMR spectrum (Figure 6) of compound Q_5 showed the characteristic peaks at 6.758-7.317 (m, 8H, Aromatic), 5.279 (s, 1H, -OH), 1.732-1.804 (m, 6H, -CH_2), 1.189 and 1.243 (S, 2H, -NH). Molecular ion peak was found at m/z 345.4 in its mass spectrum (Figure 6). CHNO analysis is found to be C-68.13, H-5.72, N-10.36 and O-15.78.

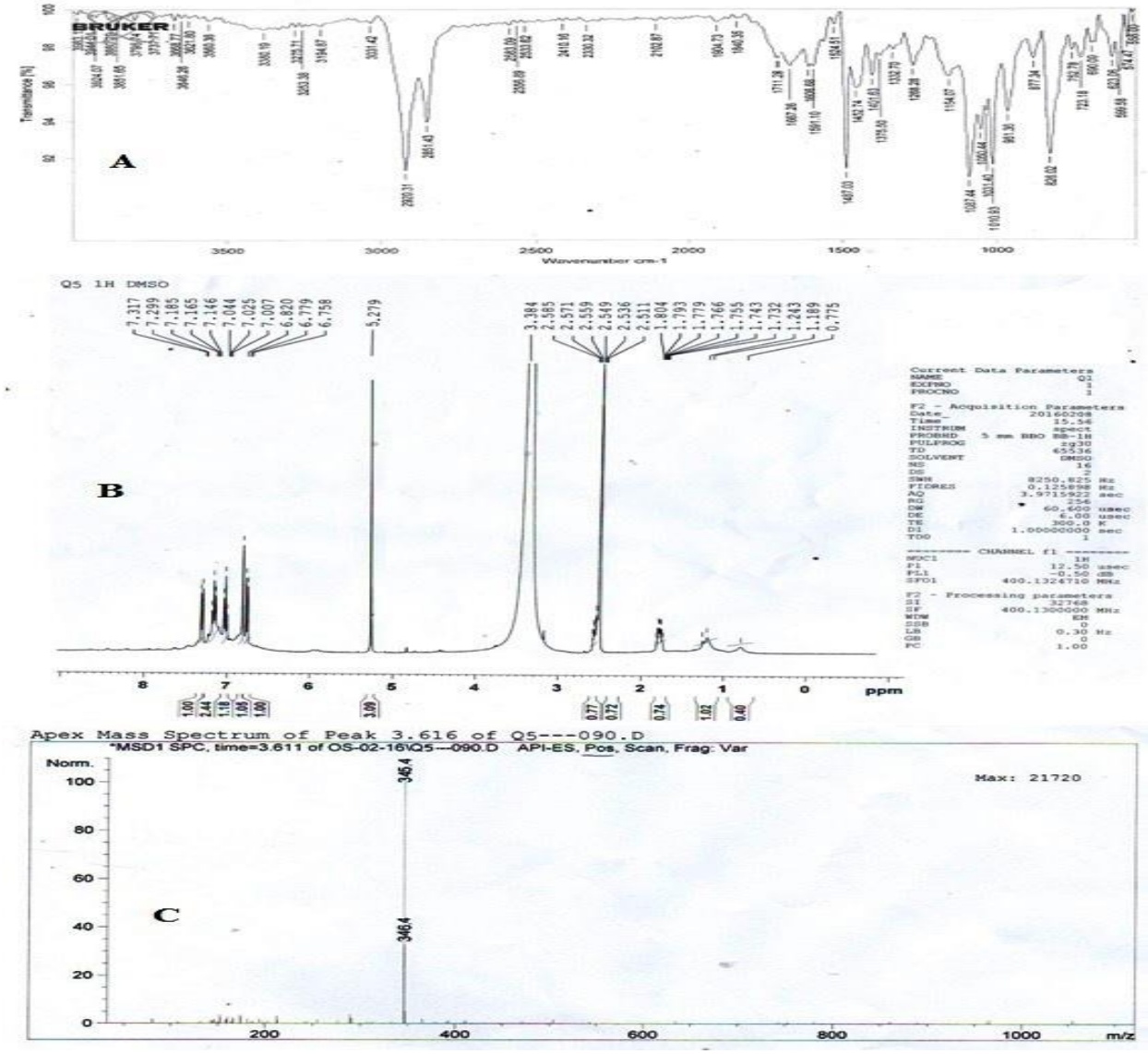


Figure 6. Compound Q5 analysis: A. FTIR Spectra, B. ^{1}H NMR Spectra, C. Mass Spectra of compound Q5.

3.2. *In-silico* methods

The application of computational technology during drug discovery and development offers considerable potential for reducing the number of experimental studies required for compound selection, improves the success rate, assess the physicochemical, biological and toxic properties of compounds at the early stages of discovery and development. They are extremely fast and cost efficient and can be applied even when a compound is not physically available.

3.3. Molinspiration

It offers free on-line services for calculation of important molecular properties as well as prediction of bioactivity score for the most important drug targets [20-21] (Table 1). The data in table 1 confirms that all the synthesized quinazolines have no violations as per Lipinski's rule. Hence, all the synthesized compounds have drug likeness.

Table 1. Molecular properties by using Molinspiration.

Code	mi Log P	Total polar surface area	No. of H-bond acceptors	No. of H-bond donors	No. of violations	No. of rotatable bonds	Volume	Drug-likeness
Q1	3.71	59.01	5	2	0	4	388.78	0.550
Q2	3.62	71.0	5	2	0	4	348.06	0.300
Q3	4.86	52.53	3	2	0	2	324.04	0.247
Q4	3.51	52.53	3	2	0	2	296.97	0.299
Q5	3.00	92.99	5	4	0	2	313.00	0.327
Q6	3.42	144.18	9	2	0	4	343.64	0.521
Q7	2.94	111.46	7	4	0	6	397.70	0.580
Q8	6.07	52.53	3	2	0	2	351.11	0.450
Q9	4.40	52.53	3	2	0	2	330.09	0.515
Q10	3.00	92.99	5	4	0	2	313.00	0.490

3.4. PASS

Novel pharmacological actions can be found for title compounds on the basis of computer program PASS. It compares the structure of a new compound with structures of well-known biologically active substance and therefore, it is possible to estimate if a new compound may have a particular effect, this approach can be used at the earliest stage of investigation [22]. Based on the prediction data, it betrays all the synthesized compounds have probability to be active towards inflammation, Antineoplastic and Alzheimer's disease treatment. Hence, we further went for *in-vitro* anti-inflammatory activity to find the potency of the compounds (Table 2).

3.5. Anti-inflammatory Activity [23]

The synthesized compounds were screened for anti-inflammatory activity (Gelatin zymography method) by the detection of NMT-2 and NMT-9 using tetracycline hydrochloride as a positive control and tonsile sample as negative control (Table 3 and Figure 7).

Table 2. Predicted biological activities by PASS Software.

Code	Anti-inflammatory		Anti-neoplastic		Alzheimer's disease treatment	
	Pa	Pi	Pa	Pi	Pa	Pi
Q1	0.627	0.055	0.402	0.103	0.472	0.034
Q2	0.509	0.027	0.497	0.072	0.444	0.020
Q3	0.539	0.051	0.411	0.014	0.402	0.010
Q4	0.552	0.014	0.400	0.104	0.504	0.012
Q5	0.503	0.030	0.442	0.052	0.498	0.028
Q6	0.595	0.014	0.490	0.094	0.515	0.015
Q7	0.495	0.032	0.452	0.105	0.486	0.030
Q8	0.610	0.051	0.486	0.075	0.540	0.015
Q9	0.580	0.094	0.494	0.060	0.460	0.025
Q10	0.515	0.062	0.440	0.025	0.458	0.042

Pa: Probability to be active; **Pi**: Probability to be inactive.

Table 3. Anti-inflammatory activity of synthesized compounds Q1-Q4.

Sample Name	Anti- inflammatory activity against MMP-2(%)	Anti-inflammatory activity against MMP-9(%)
Q1	85	88
Q2	75	80
Q3	80	90
Q4	88	92
Q5	86	90
Q6	80	85
Q7	78	82
Q8	90	96
Q9	84	90
Q10	88	94
Positive Control	100	100
Negative Control	10	10

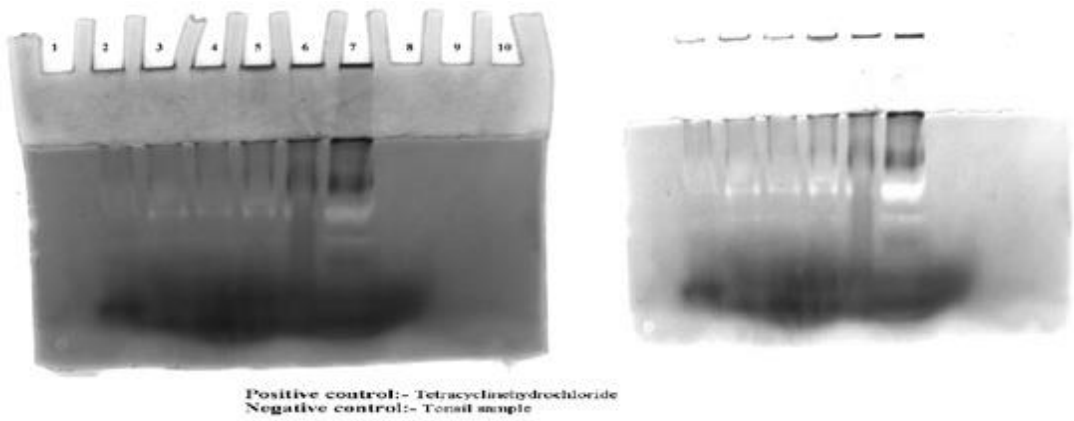


Figure 7. Anti-inflammatory activity of quinazoline-2-imine derivatives Q1-Q10.

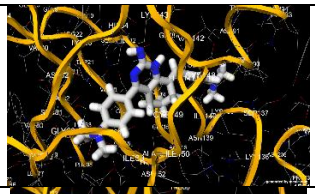
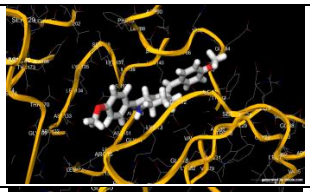
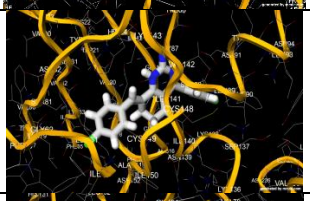
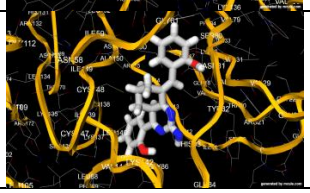
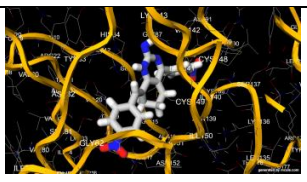
From the results of anti-inflammatory activity, it revealed that the compounds Q1-Q10 have better effect against inflammation as compared with the standard tetracycline hydrochloride. Among the all novel compounds, Q8, Q10, Q3, Q4 & Q5 showed better activity than the remaining quinazolines. The anti-inflammatory activity of these quinazolines established by docking with TGF beta receptor type 1, it is one of the cytokine receptor responsible for the release of prostaglandins which causes inflammation.

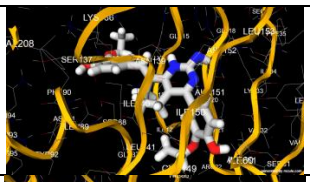
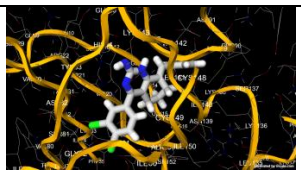
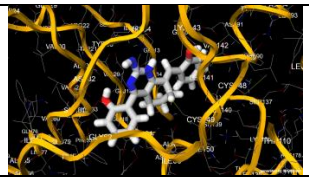
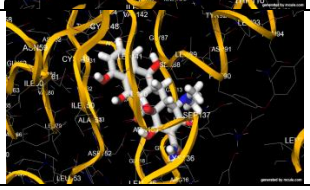
3.6. Docking studies

The novel compounds were subjected to molecular docking studies against enzyme TGF beta receptor type 1 [25]. Cytokines are large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system. Cytokines are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis. Some cytokine receptors belong to the immunoglobulin super family such as IL-1R alpha, IL-1R beta, IL-6R alpha, SCFR, c-kit, TNF receptor family, chemokine receptors, and TGF-beta receptors. TGF-beta may contribute to tumor pathogenesis by direct support of tumor growth, self-renewal of glioma initiating stem cells and inhibition of anti-tumor immunity. Inhibitors of TGF-beta signaling reduce viability and invasion of gliomas in animal models and show promises as novel, potential anti-tumor therapeutics. TGF-beta superfamily of cytokines binds to receptors at the cell surface, and recruit two type I receptors and two type II receptors forming a tetrameric complex.

Activated TGF-beta superfamily receptors induce a series of phosphorylation cascade, from receptor phosphorylation to subsequent phosphorylation and activation of downstream signal transducer R-Smads (receptor-activated Smads). Phosphorylated R-Smads form a heteroligomeric (often trimeric) complex with Smad4 (Co-Smad). The Smad complex is imported into the nucleus and regulates the expression of target genes by direct binding to the target gene promoter and/or through the interaction with transcriptional cofactors in a cell-type-specific manner [24].

Table 3. Docking score of novel compounds against TGF beta receptor type 1.

Compound	Docking Score	Docking Pose	Compound Code	Docking Score	Docking Pose
Q1	-9.1		Q2	-8.4	
Q3	-9.5		Q4	-10.3	
Q5	-9.7		Q6	-9.4	

Q7	-9.3		Q8	-10.5	
Q9	-9.6		Q10	-10.0	
Tetracycline	-11.2				

From the above docking score table, the standard drug tetracycline hydrochloride has docking score -11.2, similarly the synthesized novel compounds also showed better docking score as compared with standard. The compounds like Q8, Q10 and Q4 showed good pose to the receptor as compared with other quinazolines.

4. Conclusion

The synthesized compounds showed characteristic absorption peaks in FT-IR, ^{1}H NMR & Mass spectrum. The *in-silico* methods reveal that the compounds are obeying the Lipinski's rule and they are not having good drug likeness properties. The results of online PASS software showed anti-inflammatory activity to quinazoline derivatives it helps in further screening of anti-inflammatory activity. In the pharmacophore, due to the presence of functional groups like amino, chloro, methoxy and hydroxyl groups in aromatic ring, the compounds Q10, Q8, Q3, Q4 & Q5 exhibited more potent activity as like standard drug.Further docking studies of all novel quinazolines also well supported to its activity by posing to TGF beta receptor type 1. The study revealed the necessity of synthesizing many more quinazoline derivatives with various aldehydes. Such compounds may emerge as much more potent anti-inflammatory compounds as compared with marketed drugs by acting on TGF beta receptor type 1

5. Future perspective

Use of *insilico* methods has a wider application to reduce the experimental studies, increases success rate in drug designand development by appropriate compound selection among the synthesized compounds. Development of the compounds containing electron donating groups on pharmacophore plays an important role in inflammation deserve further investigation.

6. Conflict of Interest

The author(s) report(s) no conflict(s) of interest(s). The author along are responsible for content and writing of the paper.

7. Acknowledgment

NA

8. References

1. Haseena Banu B, Bharathi K, KVSRG Prasad. Synthesis, characterization and evaluation of *in-vitro* antioxidant and anti-inflammatory activity of 2-(4-oxo-2-phenylquinazolin-3(4H)-yl) substituted acetic acids. IOSR Journal of Pharmacy 2012; 2(1): 097-104.

2. Aslak C M, Jayalakshmi B, Balasubramaniam A. Synthesis and Pharmacological Evaluation of New 4-

Aryl-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-thiones. Indian Journal of Pharmaceutical Education and Research 2012; 46(3): 206-210.

3. Gnana Ruba Priya M, Girija K. *In-vitro* study of anti-inflammatory and antioxidant activity of 4-(3h)–quinazolinone derivatives. Rasayan Journal of Chemistry 2011; 4(2): 418-424.

4. Mosaad Mohamed S, Mohsen Kamel M, Marwa Ahmed F. Synthesis, biological evaluation and molecular docking of quinazoline-4(1h)-one derivatives as anti-inflammatory and analgesic agents. Acta Poloniae Pharmaceutica-Drug Research 2011; 68(5) 665-675.

5. Hemalatha K, Girija K. Synthesis of some novel 2,3disubstituted quinazolinone derivatives as analgesic and antiinflammatory agents. International Journal of Pharmacy and Pharmaceutical Sciences 2011; 3(2): 103-106.

6. Balakumar C, Lamba P, Raghuram Rao A. Synthesis, anti-inflammatory evaluation and docking studies of some new fluorinated fused quinazolines. European journal of medicinal chemistry. 2010; 45: 4904-4913.

7. Safinaz Abbas E, Nagwa Abdel Gawad M, HananGeorgey H. New Quinazolinone Derivatives: Synthesis, Anti-inflammatory and Antitumor Activities. International Journal of ChemTech Research 2010; 2(3): 1560-1578.

8. Aslak C M, Jayalakshmi B, Balasubramaniam A. Synthesis and Pharmacological Evaluation of New 4-Aryl-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-thiones. Indian Journal of Pharmaceutical Education and Research 2012; 46(3): 206-210.

9. Rajveer CH, Kumaraswamy D, Sudharshini S. Synthesis of some 6-bromo quinazolinone derivatives for their pharamcological activities. International Journal of Pharma and Bio Sciences. 2010; 1(3): 1-10.

10. Mani Chandrika P, Yakaiah T, Raghu Ram Rao A. Synthesis of novel 4,6-disubstituted quinazoline derivatives, their anti-inflammatory and anti-cancer activity (cytotoxic) against U937 leukemia cell lines. European Journal of Medicinal Chemistry 2008; 43: 846-852.

11. Tutuk B, Suko H. Synthesis and Molecular Docking Study of 4-Chlorophenylquinazoline-4-[3h]-One Derivatives as COX-2 Inhibitor. International Journal of Pharmaceutical and Clinical Research 2016; 8(12): 1605-1609.

12. Jahangir A, Ozair A, Javed Naim M. Recent investigations on Quinazoline Scaffold. International Journal of Advanced Research 2015; 3(12): 1656-1664.

13. Kumar Nallasivan P, Jayakar B, Gopal N. Anti-inflammatory activitiy of novel pyrazoline containing quinazolinone derivatives. Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry 2015; 3(1): 31-38.

14. Ibrahim MS, Abo-Kul M, Moustafa Soltan K. Synthesis and anti-inflammatory activity of new 2-arylidenehydrazinyl-quinazolinone and 3-amino-triazoloquinazolinone derivatives. Asian Journal of Research in Chemistry and Pharmaceutical Sciences 2013; 1(2): 59-70.

15. Arvind Kumar Singha, Lohanib M. Synthesis, Characterization and Anti-Inflammatory Activity of Some 1, 3,4 -Oxadiazole Derivatives. Iranian Journal of Pharmaceutical Research 2013; 12(2): 319-323.

16. Triveni S, Rajasekhar KK, Naresh Babu C. Synthesis, Characterization and Evaluation of Anticancer Activity of Some 7-(Substituted Benzylidene)-3-Aryl-2, 3, 4, 5, 6, 7-Hexahydro Indazol-1-Yl(Pyridin-4-Yl)Methanones. Inventi Rapid: Medicinal Chemistry 2014; 2014(2): 1-6.

17. Ramesha P, Srinivasulua D, Subba Rao D. An efficient and economic synthesis of new quinazolin-4-(3H)-one derivatives and their anti-inflammatory activity. Scholars Research Library-Der Pharmacia Lettre 2012; 4(5): 1344-1351.

18. Chatrasal Singh R, Shiwani S. Synthesis, Characterization, and Anti-Inflammatory Activity of Newer Quinazolinone Analogs. Journal of Pharmaceutics 2012; 2013: 907525.

19. Nareshbabu C, Shankarananth V, Rajasekhar KK. Synthesis, Characterisation and Anti-Tubercular Activity of Some New 3,5-Disubstituted-2,4-Thiazolidinediones. Asian Journal of Pharmaceutical and Clinical Research 2013; 6(Suppl 5): 29-33.

20. Molinspiration, Chemoinformatics. Web: http://www.molinspiration.com, Accessed on 05-01-2018.

21. Calculation of Molecular Properties and Bioactivity Score. Web: http://www.molinspiration.com/cgi-bin/properties, Accessed on 08-01-2018.

22. PASS online. Web: http://www.pharmaexpert.ru/passonline/. Prediction of bioactivity score, accessed on 10-01-2018.

23. Stromgaard K, PovlKrogsgaard-Larsen, Madsen U. Textbook of Drug Design and Discovery, Fifth Edition, CRC Press, Taylor & Francis Group Publishers, 2017.

24. Mechanism of TGF beta receptor type 1 (Cytokine receptors). Web: www.sinobiological.com, accessed on 10-01-2018.

25. Docking of synthesized novel quinazolines against TGF beta receptor type 1. Web: https://mcule.com/apps/1-click-docking, accessed on 12-01-2018.