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MOLECULAR MODELLING DESIGN AND OPIOID BINDING AFFINITY EVALUATION OF NEW 4-CHROMANONE DERIVATIVES

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ABSTRACT

The pharmacotherapy treatment of pain is an active and motivated area of investigation for treatment with free side effects. This paper presents the docking ability of twenty-five analogues of 4-Chromanone derivatives inside the crystal structure of μ opioid receptor to estimate the binding affinity of each derivative. Molecular modelling design approach applied to identify the effective substation position with generation of 989 novel 4-Chromanone derivatives. The final result of the most active twenty novel 4-Chromanone derivatives with docking affinity range (-9.89 to -9.34) kcal/mol were selected as promising hit ligand drugs comparing with morphine docking affinity at (-6.02) kcal/mol.

Keywords: Molecular modelling, docking affinity, analgesic activity, scaffold lead

INTRODUCTION

Pain (or in particular chronic pain) remains the most significant an ongoing global health problem and it is the essential reason why people need medical care leading to decrees the productivity and life quality with socioeconomic problems. Nowadays, there are many available efficient analgesics and painkiller drugs like opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) used in pain treatments, but the main limitation reason of use in therapy is related to their various side effects (**Verma *et al.*, 2018**). For that, there is a serious need to design and discover new substitutional drugs free of undesirable side effects (**Yin *et al.*, 2016**). Moreover, the mechanism of pain relief (analgesic or antinociceptive) mainly is involved with the activation of opioid receptor (all four types) by endogenous or exogenous ligands accompanying with many physiological and behavioral effects such as sedation, euphoria, anxiety, respiratory depression, and gastrointestinal transit inhibition (**Balcha & Abdela, 2017; Dahan *et al.*, 2018**). Chromans (or chromenes) are unique class of bioactive compounds consisting of benzene and pyran fused ring called benzopyrans. The flavones family includes isoflavones, flavonoids, and coumarins have been intensively studied as constituents containing benzopyran ring (**Hu *et al.*, 2016**). Chromene derivatives possess various pharmacological activities such as antitubercular, antivascular, antimicrobial, anti-inflammatory, antioxidant, TNF-α inhibitor, antitumor, antiviral, antifungal, anticoagulant, antispasmolytic, estrogenic, anthelminthic, anti-HIV, herbicidal, analgesic, and anticonvulsant activity (**da Silva *et al.*, 2014; Fadda *et al.*, 2012; Hussain *et al.*, 2014; Mladenović *et al.*, 2010; Mungra *et al.*, 2011; Ratnakar Reddy *et al.*, 2014; Sankar *et al.*, 2017**). Moreover, 4-Chromanone (or chroman-4-one) is the most common name for the dihydrobenzopyranone. Up to 1971, many of this compounds group were indexed in Chemical Abstracts bulletin as 4-chromanones, but since that year the name has been changed to 2,3-dihydro-4H-1-benzopyran-Cones **(Butler *et al.*, 2010; Wen *et al.*, 2016**).

In the field of combinatorial chemistry, scaffold lead hopping is a modern applicable approach refers to the attempt to discover of new medical molecules with higher better or similar bioactivities to the original molecules structures (**Zhao, 2007**). Many computational methods have been applied to design and generate multi molecules structures by chemical group replacement to achieve new compound similar in skeleton to the active drug to with better activities (**Aysha *et al.*, 2014; Brown & Jacoby, 2006**). These methods includes and subdivide to virtual screening, de novo molecular design, topology similarity, pharmacophore search and shape similarity search **(Eckert & Bajorath, 2007; Khedkar *et al.*, 2007; Klebe, 2006**). In particular, the main aims of chemical group replacement to prevent many biological, chemical, or even intellectual side effects associated to the scaffold of currently used drugs (**Abd Razik *et al.*, 2020; Mehdy *et al.*, 2018**). In addition, this approach is usually used to enhance ADMET (absorption, distribution, metabolism, excretion, and toxicity) molecule profile and the potency of targeted activity by generating series of molecules as an analogous of the active drug (**Lo *et al.*, 2018**). In this paper, a series of 4-Chromanone analogues with analgesic activity was collected from literatures and there binding affinity inside μ opioid receptor was computationally evaluate (**Higgs *et al.*, 2013; Orazbekov *et al.*, 2018**). Next, model evaluation and chemical group replacement at selected position was applied to create new 4-Chromanone analogues with higher antinociceptive activity and lower undesirable side effects. The higher active twenty novel 4-Chromanone derivatives were selected as promising hit ligand drugs comparing with best drug for pain treatment (Morphine).

COMPUTATIONAL METHOD

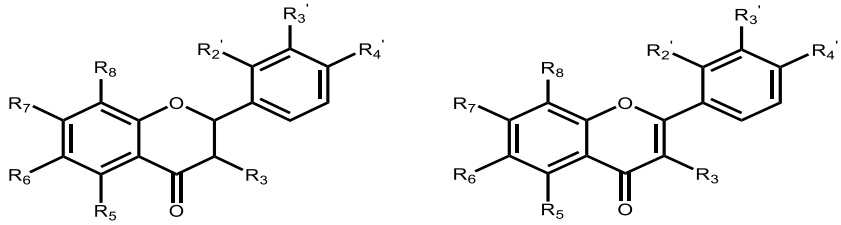
A total of 25 4-Chromanone derivatives structures was obtained from literatures and the 3D derivative conformations was drawn by using ChemDraw16.0 program under ChemOffice package (ChemOffice, 2016). Next step, geometry optimization was perform by MM+ force field using Hyperchem program version 8.0 (**Coleman & Arumainayagam, 1998**) and saved as .mol file format in sprite files. Furthermore, an additional geometry optimization by semi-empirical approach was applied for RM1 (Recife Model 1) (**Rocha *et al.*, 2006**). To this step the lowest energy conformation of each molecule is saved as .sdf file format and optimized by using Spartan 14.0 software under windows (Spartan, 2014) with Monte Carlo approach with 100 cycles of optimization, 1000 interactions (**Cohen, 1996**). Molecular modeling design and molecular docking study were performed by using Glide docking software (Maestro 11.4) under Schrodinger package software (Schrodinger, 2018) for the preparation, minimization and docking studies running on Windows 7 Service Pack 1 operating system on Hp Precision T-1580 workstation (Intel (R) Core (TM) i7 CPU 896 @ 3.5GHz, 16 GB RAM, 1 TB HD). The crystal structures of active μ opioid receptor and agonist ligand was obtained from Protein Data Bank under PDB code: 5C1M with crystallographic resolution of 2.1. The receptor preparation steps were applied by ProPrep tool to optimize and protein minimization. This tool used to fill up any missing amino acids, removing of water molecules and ligands with improving of structure resolution. Ligand preparation applied by using LigPrep tool before docking to identify the best orientation and probable ionization position with adding hydrogen atom to achieve lowest energy conformations of each ligand by using OPLS 2005 force field. The size of receptor grid box adjusted to 50 × 50 × 50 Å with a partial atomic charge of 0.27 and during

docking process the receptor kept rigid and ligands were flexible. The best docked orientation and RMSD between protein crystal structure was saved and in order to generate several derivatives with diverse fragment the automated fragment replacement processes was applied. All derivatives were generated and saved by Custom R-Group Enumeration approach under Maestro software by the replacement of hydrogen atom in compound 6.

RESULTS AND DISCUSSION

Over the past decades, opioid receptor has received the most permanent attention as a prominent target for new drug design and discovery due to its essential role in mediating of multi pharmacological issues subjected to behavioral and neurophysiological, including addictive behavior, pain sense, and gastrointestinal motility physiology (**Pasternak, 2014**). Thus, there has been intensive focus on the design and discovery of novel active ligands toward opioid receptor with high potential efficient therapeutics (**Greedy *et al.*, 2013**) . The successful crystallization process of μ opioid receptor structure in 2015 inspire the ability to estimate the structure activity relationships and binding affinity between ligand and human μ opioid receptor as the target to achieve new painkiller drugs (**Huang *et al.*, 2015**). In this present work, the theoretical binding affinity application and molecular modeling design combination approaches for the discovery of novel molecules as agonist ligands at active site of human μ opioid receptor. The result of these approaches is a total of twenty-five 4-Chromanone derivatives collected from literatures and docked inside active site of human μ opioid receptor to evaluate the binding affinity of each molecule as shown in table 1.

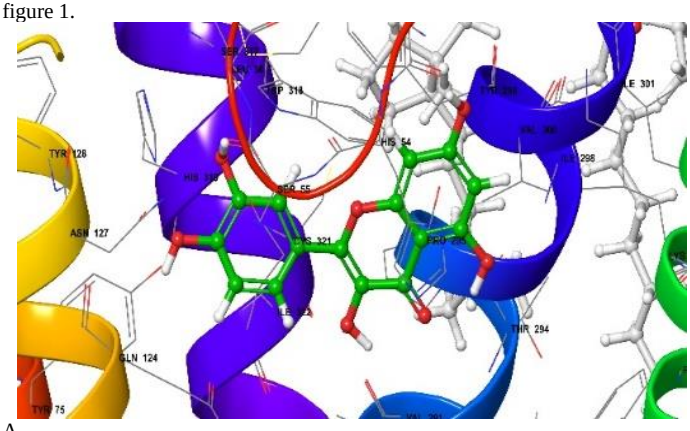
Table 1 Docking score of substituted 4-Chromanone derivatives collected from literatures



A B

Compound	Moiety	R_3	R_5	R_6	R_7	R_8	R_2`	R_3`	R_4`	Docking Score in kcal/mol
1	A	H	H	H	H	H	H	H	H	-6.84
2	A	H	OH	H	OH	H	H	OH	OCH_3	-6.95
3	A	H	OH	H	OH	H	H	H	OH	-6.09
4	B	H	H	H	H	H	H	H	H	-6.38
5	B	H	OH	H	OH	H	H	OH	OCH_3	-7.63
6	B	OH	OH	H	OH	H	H	OH	OH	-8.36
7	B	H	OH	H	OH	H	H	H	OH	-6.96
8	B	H	OH	H	OH	H	H	H	H	-7.24
9	B	H	H	CH_3	H	H	H	H	H	-6.94
10	B	H	H	NO_2	H	H	H	H	H	-6.22
11	B	H	H	F	H	H	H	H	H	-7.03
12	B	H	H	Cl	H	H	H	H	H	-6.57
13	B	H	H	CH_3	H	H	H	CH_3	H	-5.90
14	B	H	H	CH_3	H	H	H	Br	H	-5.98
15	B	H	H	H	H	H	NO_2	H	H	-4.68
16	B	H	H	H	H	H	H	NO_2	H	-6.12
17	B	H	H	H	H	H	H	Cl	H	-6.89
18	B	H	H	H	H	H	H	Br	H	-7.12
19	B	H	H	H	H	H	H	CH_3	H	-6.50
20	B	H	H	H	H	H	H	H	NO_2	-5.24
21	B	H	H	H	H	H	H	H	F	-5.65
22	B	H	H	H	H	H	H	H	Br	-5.59
23	B	Br	H	H	H	H	H	NO_2	H	-6.78
24	B	Br	H	Br	H	H	H	H	H	-6.63
25	A	Br_2	H	H	H	H	H	H	H	-4.32
Morphine	-	-	-	-	-	-	-	-	-	-6.02

In this table, docking score affinity range is between -4.32 kcal/mol for compound 25 to -8.36 kcal/mol for compound 6 with -6.02 kcal/mol for morphine to compare as positive control. These findings refer to the high interesting affinity of compound 6 to bind inside the active site pocket inside opioid receptor comparing with surrounded by the most important amino acids figure 1.



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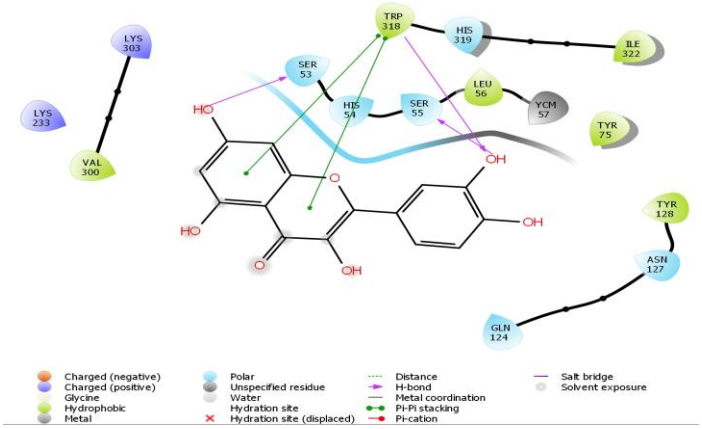
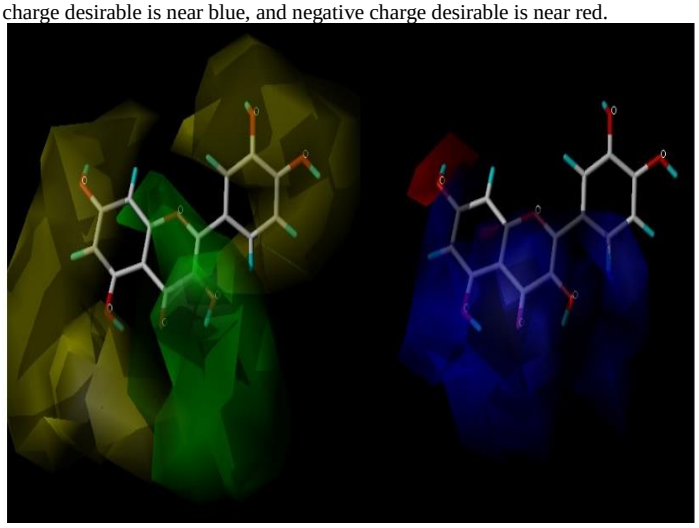


B

Figure 1 Compound 6 inside μ opioid receptor active site surrounded by amino acids (A) Compound 6 as ball and stick, receptor as ribbon. (B) Ligand interaction view of compound 6

Inside receptor active site, compound 6 bind to TRP318 by tow Pi-Pi stacking interaction bond with both aromatic rings and forming H-bond with hydroxyl group at R_3` position. An additional two H-bond formed between SER53 and SER55 with hydroxyl groups at $R_7$ and $R_3$` positions, respectively. Moreover, compound 6 inclosed by the following receptor active site amino acids: SER53, HIS54, SER55, LEU56, TYR75, GLN124, ASN127, TYR128, LYS233, VAL300, LYS303, TRP318, HIS319, and ILE322. Based on docking score result and QSAR model result evaluation, compound 6 was select as lead hit molecule for the next step to apply group replacement at selected effective group position. Figure 2 shows compound 6 (the best active compound) with desirable and undesirable reigns colored in green and yellow contours. These two reigns are labeled and colored depending on the destination of each area as following: Steric bulk undesirable is near yellow, steric bulk desirable is near green, positive charge desirable is near blue, and negative charge desirable is near red.



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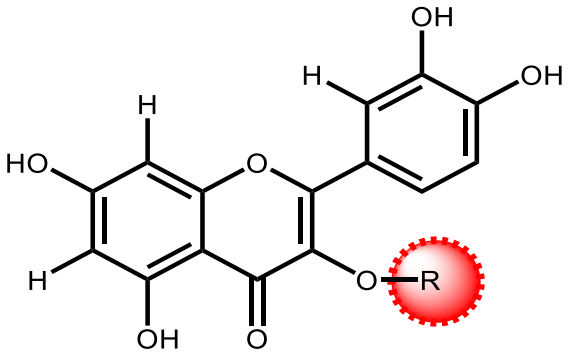
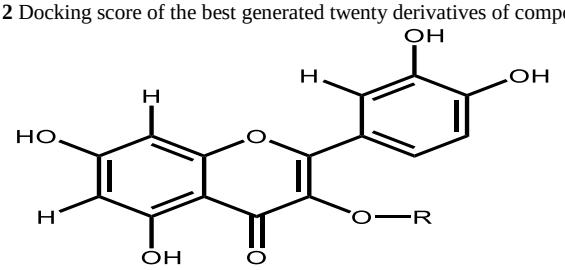


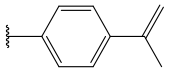
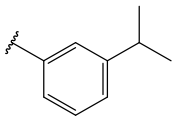
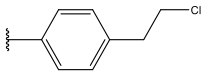
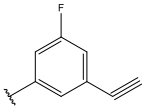
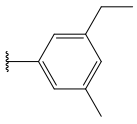
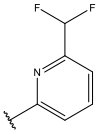
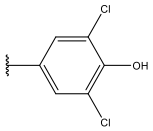
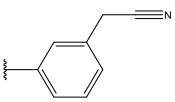
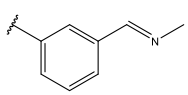
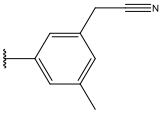
B

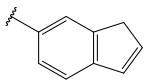
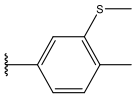
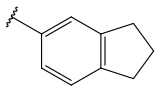
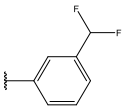
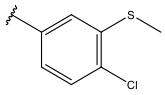
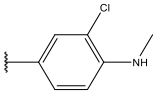
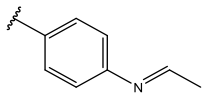
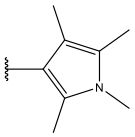
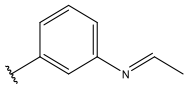
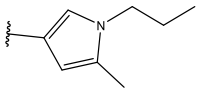
Figure 2 Compound 6 (A) with desirable and undesirable contours reigns. (B) Substation position in red shaded cycle.

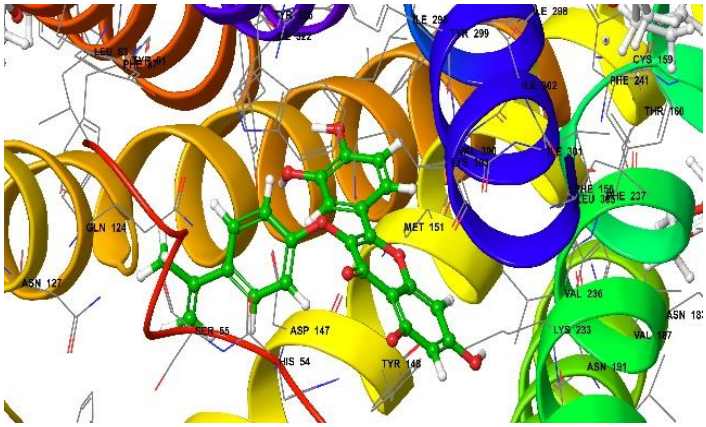
The green area is referring to the described best reign to replace with promising potency. From this point, hydroxyl group at R_3 position was select to be replaced by many deferent chemical groups from database. After performing molecular group replacement generation, a total of 989 new 4-Chromanone derivatives were docked, recorded, and the higher best twenty molecules are listed dissenting in table 2. Among all derivatives, a total of sixty-eight compound were better than morphine. The substituted group replacement by alpha-methylstyrene group at position R3 result a high active compound N01 with high docking score -9,89 kcal/mol. This increasing in binding affinity companied with very good orientation inside the receptor active site and inclosed by important amino acids figure 3.

Table 2 Docking score of the best generated twenty derivatives of compound 6



Compound	R	Docking Score in kcal/mol	Compound	R	Docking Score in kcal/mol
N01 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(4-(prop-1-en-2-yl)phenoxy)-4H-chromen-4-one		-9.89	N11 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(3-isopropylphenoxy)-4H-chromen-4-one		-9.56
N02 3-(4-(2-chloroethyl)phenoxy)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one		-9.88	N12 2-(3,4-dihydroxyphenyl)-3-(3-ethynyl-5-fluorophenoxy)-5,7-dihydroxy-4H-chromen-4-one		-9.54
N03 2-(3,4-dihydroxyphenyl)-3-(3-ethyl-5-methylphenoxy)-5,7-dihydroxy-4H-chromen-4-one		-9.86	N13 3-((6-(difluoromethyl)pyridin-2-yl)oxy)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one		-9.52
N04 3-(3,5-dichloro-4-hydroxyphenoxy)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one		-9.85	N14 2-(3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)phenyl)acetonitrile		-9.50
N05 (E)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(3-((methylimino)methyl)phenoxy)-4H-chromen-4-one		-9.75	N15 2-(3-((2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)-5-methylphenyl)acetonitrile		-9.44

N06 3-((1H-inden-6-yl)oxy)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one		-9.75	N16 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-(4-methyl-3-(methylthio)phenoxy)-4H-chromen-4-one		-9.41
N07 3-((2,3-dihydro-1H-inden-5-yl)oxy)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one		-9.74	N17 3-(3-(difluoromethyl)phenoxy)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one		-9.38
N08 3-(4-chloro-3-(methylthio)phenoxy)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one		-9.73	N18 3-(3-chloro-4-(methylamino)phenoxy)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one		-9.37
N09 (E)-2-(3,4-dihydroxyphenyl)-3-(4-(ethylideneamino)phenoxy)-5,7-dihydroxy-4H-chromen-4-one		-9.69	N19 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-((1,2,4,5-tetramethyl-1H-pyrrol-3-yl)oxy)-4H-chromen-4-one		-9.35
N10 (E)-2-(3,4-dihydroxyphenyl)-3-(3-(ethylideneamino)phenoxy)-5,7-dihydroxy-4H-chromen-4-one		-9.65	N20 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-((5-methyl-1-propyl-1H-pyrrol-3-yl)oxy)-4H-chromen-4-one		-9.34



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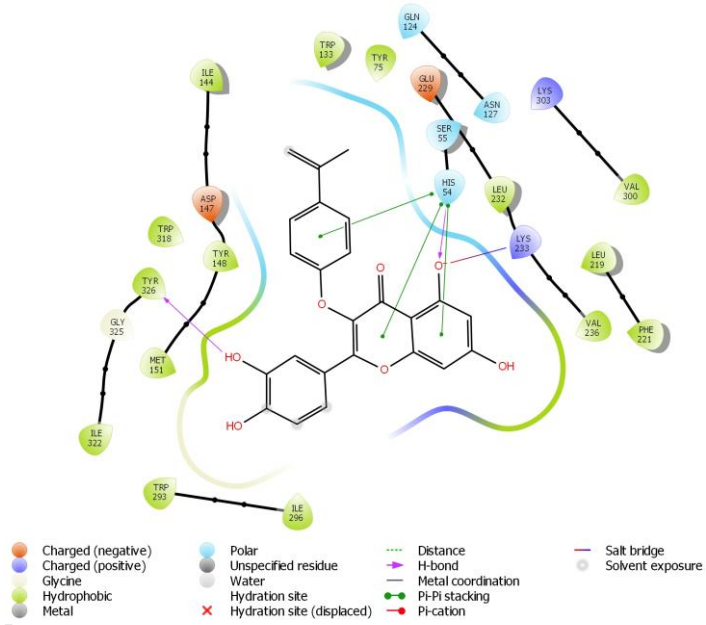

B

Figure 3 Compound N01 inclosed by most important amino acids inside human μ opioid receptor active site (A) Compound N01 as ball and stick, receptor as ribbon. (B) Ligand interaction view of compound N01.

Inside active site compound N01 bind by three Pi-Pi stacking interactions HIS54 from three aromatic rings. Another two interactions with hydroxyl group by H-bond interactions with LYS233 and HIS54. Moreover, all the active important amino acids inclosed with this compound supported with the previous interactions. The existing of these interactions helps to increase the binding affinity and activity of any compound inclosed inside active site. In contrast, between many interesting and well-known μ opioid receptor active ligands, these twenty compounds consider as new novel chemical scaffolds. It is referring to that hits selection group replacement molecule approaches usually will provide better active compound than the compounds in virtual screening models.

CONCLUSION

In drug design, scaffold hopping is one of the best important approach in molecular discovery and design to improve potency or binding affinity selection. In this present paper, the result of applying this concept was a novel 4-Chromanone analogues with higher pharmacological profile and binding affinity inside active site of human μ opioid receptor. This is materialized by high binding affinity among a total of sixty-eight compounds better than morphine within a range of (-9.89 to -9.34) kcal/mol for the highest twenty compounds promoted with Pi-Pi stacking and H-bond interactions. Further biological and pharmacological evaluation is required to understand the side effects of all novel portentous drugs.

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