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Design and synthesis of novel 4-aminophenazone Schiff bases by grinding technique as prospective anti-inflammatory agents

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ABSTRACT

Schiff bases are biologically diverse molecules with vast pharmacological activities and have been an area of interest in medicinal chemistry. Recently, this class also attributed new targets for drug development and research. The present study reveals the design and synthesis of the novel Schiff bases as prospective anti-inflammatory agents from the combination of 4-aminopyrazone with different aldehydes with a simple and effective grinding technique to produce different yellow-shaded products. The compounds formed were analyzed by IR spectra and ^{1}H-nuclear magnetic resonance. Synthesized derivatives were evaluated *in silico* using docking studies to predict phosphodiesterase 7 (PDE7) inhibition and to investigate the binding interactions of the synthesized derivatives with active site residues of PDE7. These compounds showed appreciable binding interactions with PDE7 protein and good drug-like properties.

INTRODUCTION

Innovation of potent and newer analogs of molecules with already established activities form a research key in the pharamaceutical field. Biological activities of various organic molecules are characterized by their structural attributes which result in certain activities of the parent molecule while others are the result of the associated type, orientation type, and of additives modification. Bringing about modification by manipulating the basic compound structures serves to enhance the activity of the compound and also removes toxicity associated with a basic structure (Cunha *et al*., 2005; Jawher *et al*., 2011; Mohanram and Meshram, 2014).

Prostaglandins and various inflammation mediators can cause pyrexia and pain in the body. Nonsteroidal anti-inflammatory drugs (NSAIDs) can effectively block the synthesis of these mediators. Ancient history has proved them to be as major therapeutic potentials for their use in the commercial market and clinical practice. NSAIDs are used for the treatment of diseases like gout, arthritis, and asthma (Rainsford, 2007). As they cause nonselective inhibition of both Cyclooxygenase (COX-1) and COX-2 isoforms of the cyclooxygenase enzymes, their long-term administration leads to renal disorders,bleeding, and gastrointestinal ulcers (Hörl, 2010).

Alternatives to NSAIDs are being searched for all over the world so that newly designed anti-inflammatory drugs are without varied side effects. The inhibition of phosphodiesterase 7 (PDE7) results in elevated Cyclic adenosine monophosphate (cAMP) levels leading to a decrease in edema, cellular inflammation, and bronchoconstriction, as well as the release of mucous. The effectiveness of the inhibitors of PDE7 enzyme has been reported recently in animal models as anti-inflammatory agents and denotes as a novel category of drugs for the management of various inflammatory diseases (Gil *et al*., 2008; Grewal *et al*., 2017a). Due to the emerging need of improved analogs, various heterocyclic compounds are synthesized, including pyrazole compounds and their derivatives as PDE7 inhibitors (Redondo *et al*., 2012). 4-Aminoantipyrine could be used as a backbone for the synthesis of pyrazolone analogs having various vital pharmacological activities. 4-Aminoantipyrines are the best known antipyrine derivatives indicated to be used in oxidative stress and also have prophylaxis in the diseases like cancer have many other medical implementations (Barnes *et al*., 2001; *et al*., 2004).

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The largest number of heterocyclic compounds are of synthetic origin, although few have also been obtained from natural resources like antibiotics, vitamins, cardiac glycoside, and alkaloids. Nowadays, chemists are paying attention to Schiff bases to discover new drugs with very few side effects, as they indicate a wide range of biological activities, which have a proved structure activity relationship of these bases (Vergne *et al*., 2004).

Recently, various methods have been Schiff base-containing derivatives that have been synthesized and evaluated for their biological activities, such as antimicrobial, anti-tuberculosis, antioxidant, anti-inflammatory, anticonvulsants, antidepressant, anxiolytic, antihypertensive, anticancer, and antifungal activities. The search for Schiff base-containing compounds with more selective activity and lower side effects continues to be an active area of argument examination in medicinal chemistry (Aboul-Fadl and Bin-Jubair 2010; Alam *et al*., 2012; da Silva *et al*., 2011; Gaber *et al*., 2018; Malik *et al*., 2018; Murtaza *et al*., 2017; Rakesh *et al*., 2015; Sondhi *et al*., 2006).

Various methods have been used for the synthesis of derivatives of Schiff bases (Akhter *et al*., 2017; Al Zoubi *et al*., 2016). The present paper deals with the synthesis of Schiff bases of 4-aminopyrazone by using grinding technique, followed by docking studies with PDE7 and evaluating them in future for anti-inflammatory and analgesic activities.

MATERIALS AND METHODS

Chemicals

4-Aminoantipyrine was obtained from CDH Ltd. (New Delhi, India) and other reagents were procured from Loba Chem, Merck Ltd., and SD Fine. The progress of the reaction was monitored by precoated silica gel plates 60 F_{254} (Merck). Melting points (°C) were determined with a LABINDIA melting point apparatus and were uncorrected. Fourier-transform infrared spectroscopy (FTIR) spectra were recorded on Bruker FT-IR spectrometer by using KBr disks at Chitkara College of Pharmacy. The ^{1}H-nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance II 400 Spectrometer-400MHz in $CDCl_3$ using TMS as an internal standard at Panjab University, Chandigarh.

General synthesis

A mixture of 4-aminophenazone **(1)** (0.01 moL) and different aldehydes **(2)** (0.02 moL) were ground in a pestle mortar; the mixture turned pasty after a few minutes of grinding. The grinding continued until a yellow product appeared. The mixture was left overnight. The synthesized compounds **(S1–S6)** were recrystallized from ethanol. The reaction completion was monitored by Thin Layer Chromatography (TLC).

4-(4-Bromobenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one (S1)

^{1}H NMR ($CDCl_3$): 2.5006 (*s*, 3H, −CH_3), 3.1625 (*s*, 3H, −NCH_3), 7.4475–7.4295 (*m*, 5H, Ar-H), 7.5193–7.5402 (*d*, 2H, Ar-H, *J* = 8.4), 7.7066–7.7276 (*d*, 2H, Ar-H, *J* = 8.4), 9.7021 (*s*, 1H,N=CH); IR cm^{-1}: 1,073 (Ar-Br; str), 1,370 and 1,462 (−CH_3; CH bend), 1,640 (C=N; str), 2,856–2,973 (Ar-CH; str).

4-(4-Hydroxybenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one (S2)

^{1}H NMR ($CDCl_3$): 2.4919 (*s*, 3H, −CH_3), 3.2028 (*s*, 3H, −NCH_3), 6.8180–6.7968 (*d*, 2H, Ar-H, *J*=8.48), 7.3406–7.3753 (*m*, 3H, Ar-H), 7.4281–7.4368 (*d*, 2H, Ar-H, *J* = 3.48), 7.6375–7.6163 (*d*, 2H, Ar-H, *J* = 8.48), 8.7534 (*bs*, 1H, −OH), 9.5886 (*s*, 1H, N=CH); IR cm^{-1}: 1,290 (C-O; str), 1,420 and 1,458 (-CH3; CH bend), 1,651 (C=N; str), 2,934–2,972 (Ar-CH; str), 3,420 (−OH; str).

4-(4-Nitrobenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one (S3)

^{1}H NMR ($CDCl_3$): 2.5291 (*s*, 3H, −CH_3), 3.2421 (*s*, 3H, −NCH_3), 7.3497–7.3990 (*m*, 3H, Ar-H), 7.4863–7.4907 (*m*, 2H, Ar-H), 7.9676–7.9896 (*d*, 2H, Ar-H, *J* = 8.8), 8.2401–8.2620 (*d*, 2H, Ar-H, *J* = 8.76), 9.7915 (*s*, 1H, N=CH); IR cm^{-1}: 1,345 and 1,552 (Ar-NO2; str), 1,418 and 1,460 (-CH3; CH bend), 1,642 (C=N; str), 2,851–2,926 (Ar-CH; str), 3,075–3,107 (CH; str Ar-NO2; str).

4-(3,4,5-Trimethoxybenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one (S4)

^{1}H NMR ($CDCl_3$): 2.4979 (*s*, 3H, −CH_3), 3.1592 (*s*, 3H, −NCH_3), 3.8909 (*s*, 3H, −OCH_3), 3.9202 (*s*, 6H, −OCH_3), 7.1234 (*s*, 2H, Ar-H), 7.4013–7.4258 (*m*, 2H, Ar-H), 7.4659–7.5047 (*m*, 3H, Ar-H), 9.6862 (*s*, 1H, N=CH); IR cm^{-1}: 1,234 (Ar-C-O; str), 1,393 and 1,464 (−CH_3; CH bend), 1,647 (C=N; str), 2,846–2,942 (Ar-CH; str).

1,5-Dimethyl-4-((5-nitrofuran-2-yl)methyleneamino)-2-phenyl-1,2-dihydropyrazol-3-one (S5)

^{1}H NMR ($CDCl_3$): 2.5186 (*s*, 3H, -CH_3), 3.2605 (*s*, 3H, -NCH_3), 6.9239–6.9334 (*d*, 1H, −ArH), 7.3753–7.3996 (*m*, 3H, Ar-H), 7.4896–7.5283 (*m*, 3H, Ar-H), 9.8619 (*s*, 1H, N=CH); IR cm^{-1}: 1,365 and 1,467 (−CH_3; CH bend), 1,642 (C=N; str), 2,944–3,150 (Ar-CH; str).

4-(3,4-Dimethoxybenzylideneamino)-1,5-dimethyl-2-phenyl-1,2-dihydropyrazol-3-one (S6)

^{1}H NMR ($CDCl_3$): 2.4856 (*s*, 3H, −CH_3), 3.1317 (*s*, 3H, −NCH_3), 3.9182 (*s*, 3H, −OCH_3), 3.9426 (*s*, 3H, −OCH_3), 6.9684–6.9888 (*d*, 1H, Ar-H, *J* = 8.16), 7.3013–7.3268 (*m*, 1H, Ar-H), 7.4003–7.4249 (*m*, 3H, Ar-H), 7.4536–7.4688 (*m*, 2H, Ar-H), 7.5481–7.5525 *m*, 1H, Ar-H), 9.6945 (*s*, 1H, N=CH); IR cm^{-1}: 1,268 (Ar-C-O; str), 1,364 and 1,461 (-CH3; CH bend), 1,646 (C=N; str), 2,841–3,081 (Ar-CH; str).

In silico prediction of pharmacokinetic parameters

All the synthesized molecules were analyzed for the prediction of pharmacokinetic parameters related to absorption, distribution, metabolism, and excretion (ADME) by employing FAF-Drugs4 online server; and accessed using "Lipinski's rule of 5" for drug-likeness (Lagorce *et al*., 2017).

Molecular docking studies

Docking studies were carried out for the synthesized compounds with PDE7 protein using AutoDock Vina (Trott and Olson, 2010) and the graphical user interface, AutoDock Tools

(ADT) (Morris *et al*., 2009). 2D chemical structures of the ligands were drawn using Marvin Sketch (ChemAxon. Ltd. Budapest, Hungary) and converted to 3D using Frog2 (Miteva *et al*., 2010) server, followed by thepreparation of PDBQT files using ADT. The co-crystallized information about PDE7 was taken from the protein data bank. After evaluating the number of entries, the best ligand bound complex (PDB entry: 4PM0) was selected based on maximum resolution. The PDB file of the protein was edited and the complexed inhibitor, all the water molecules as well as all non-interacting ions, were removed using PyMOL (Schrödinger, LLC). PDBQT file of protein from PDB file was generated using ADT. All the polar hydrogen atoms were added to the protein molecule and grid parameters were calculated utilizing "Grid" in ADT. The accuracy of docking procedure was checked by docking of the reference inhibitors in the active sites of PDE7. The optimized ligands were docked into the active site of the refined PDE7 models using AutoDock Vina and scored using scoring functions (Charaya *et al*., 2018; Grewal *et al*., 2017b; Sharma *et al*., 2019).

RESULT AND DISCUSSION

Chemistry

The designed molecules 4-aminopyrazone Schiff bases (S1–S6) were synthesized (Figure 1) starting from 4-aminophenazone (1) and different aldehydes (2). Physiochemical data of 4-aminophenazone Schiff bases are given in Table 1.

The disappearance of a primary amino group ($-NH_2$) stretch and appearance of absorption band at 1,640–1,650 cm^{-1} related to the ν (C=N) stretch of the Schiff base in the FTIR spectra of synthesized compounds indicates the synthesis of desired compounds. Furthermore, a prominent singlet signal of N=Cat δ 9.58–9.86 ppm in the ^1H NMR spectra confirmed the formation of title compounds (S1–S6) (Table 2).

Prediction of ADME properties

ADME parameters, including molecular weight (MW), partition coefficient (log P), distribution coefficient

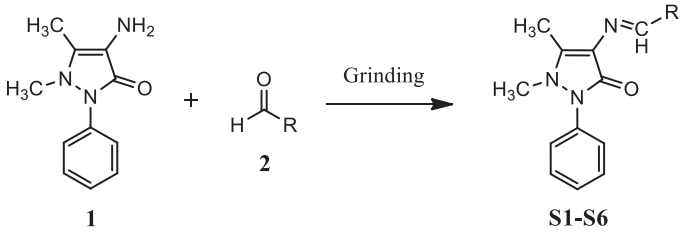
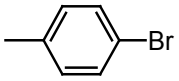
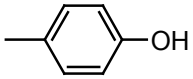
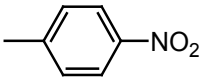
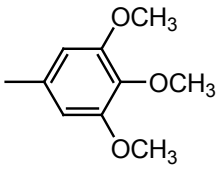
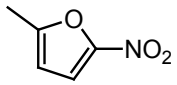
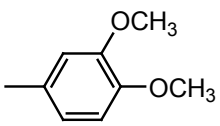


Figure 1. Synthesis of the novel series of 4-aminophenazone Schiff bases.

Table 1. Physiochemical parameters of Schiff bases of 4-aminophenazone (S1–S6).

Comp.	R	Molecular formula	% Yield	M. pt. (°C)	R_f[a]
S1		$C_{18}H_{16}BrN_3O$	78	127–128	0.57
S2		$C_{18}H_{17}N_3O_2$	75	135–136	0.62
S3		$C_{18}H_{16}N_4O_3$	72	130–132	0.54
S4		$C_{21}H_{23}N_3O_4$	80	122–124	0.60
S5		$C_{16}H_{14}N_4O_4$	75	132–133	0.48
S6		$C_{20}H_{21}N_3O_3$	80	121–122	0.58

[a]TLC Solvent: Chloroform: methanol (8:2).

(log D), water solubility (log Sw), topological polar surface area (tPSA), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), solubility (mg/L), and number of rotatable bonds (NRB), were predicted for all the compounds. All of the derivatives showed good pharmacokinetic parameters for oral bioavailability (Table 3) and drug-likeness as contrived by "Lipinski's rule of 5".

In silico docking studies

Molecular docking studies were carried out for the synthesized analogs for investigating interactions of these compounds with PDE7 and understanding the mechanism of action of the designed molecules as PDE7 inhibitors. The docking procedure was validated by comparing the binding poses obtained by docking of reference inhibitor in the binding site of PDE7 with that of the original PDB. Most of the synthesized molecules showed appreciable binding with PDE7 as determined by analysing binding interactions and binding free energy (ΔG, kcal/mol) of the selected best docked poses (Table 4). Based on the lowest binding free energy and better docking interactions, the best docked poses of all the synthesized compounds (S1–S6) were further analyzed in details by PyMOL and Biovia Discovery Studio (Dassault Systems).

The overlay pictures of all the synthesized compounds (S1–S6) with the PDB Ligand 4PM0 (2-(cyclopentylamino)-3-ethyl-7-ethynylthieno[3,2-d]pyrimidin-4(3H)-one) showed that these compounds have the similar orientation and binding pattern in the binding site of PDE7 protein as that of the co-crystallized inhibitor of PDE7 (Figure 2).

The docked pose of S2 showed various types of hydrophobic interactions including pi-pi (Tyr211 and Phe416), pi-sigma (Val380), pi-alkyl (Ile323 and Ile363), and alkyl (Pro262). Compound S2 showed two H-bond interactions between OH group of compound S2 and hydroxyl moiety of Tyr211 and carbonyl of ASn365 residues of PDE7 protein with bond length of 3.10 and 2.72 Å, respectively. The "4-hydroxyphenyl" ring of S2 protruded in the hydrophobic pocket showed interactions with Tyr211, Val380, and Phe416 residues in binding site of PDE7. The "1,2-dihydropyrazol-

Table 2. ^{1}H-NMR and FTIR spectral data for the synthesized compounds (S1–S6).

Comp.	^{1}H-NMR (δ)	FTIR νmax (cm^{-1})
S1	2.5006, 3.1625, 7.4475–7.4295, 7.5193–7.5402, 7.7066–7.7276, 9.7021	1,073, 1,370, 1,462, 1,640, 2,856–2,973
S2	2.4919, 3.2028, 6.8180–6.7968, 7.3406–7.3753, 7.4281–7.4368, 7.6375–7.6163, 8.7534, 9.5886	1,290, 1,420, 1,458, 1,651, 2,934–2,972, 3,420
S3	2.5291, 3.2421, 7.3497–7.3990, 7.4863–7.4907, 7.9676–7.9896, 8.2401–8.2620, 9.7915	1,345, 1,552, 1,418, 1,460, 1,642, 2,851–2,926, 3,075–3,107
S4	2.4979, 3.1592, 3.8909, 3.9202, 7.1234, 7.4013–7.4258, 7.4659–7.5047, 9.6862	1,234, 1,393, 1,464, 1,647, 2,846–2,942
S5	2.5186, 3.2605, 6.9239–6.9334, 7.3753–7.3996, 7.4896–7.5283, 9.8619	1,365, 1,467, 1,642, 2,944–3,150
S6	2.4856, 3.1317, 3.9182, 3.9426, 6.9684–6.9888, 7.3013–7.3268, 7.4003–7.4249, 7.4536–7.4688, 7.5481–7.5525, 9.6945	1,268, 1,364, 1,461, 1,646, 2,841–3,081

Table 3. Predicted ADME properties of the synthesized compounds (S1–S6).

Comp.	MW	log P	log D	log Sw	tPSA	HBA	HBD	Solubility	NRB
S1	370.2	2.81	3.65	−4.03	39.3	4	0	6,578.4	3
S2	307.4	1.77	2.57	−2.98	59.5	5	1	15,655.6	3
S3	336.3	1.95	2.82	−3.20	85.1	7	0	13,755.8	4
S4	381.4	2.03	2.41	−3.33	66.9	7	0	13,592.4	6
S5	326.3	3.06	1.97	−3.84	98.3	8	0	7,024.2	4
S6	351.4	3.44	2.57	−4.12	57.7	6	0	5,688.2	5

Table 4. Binding interactions and docking score (ΔG) of the synthesized derivatives with PDE7.

Comp.	H-bond interactions		Residues involved in hydrophobic interactions	ΔG
	Residues	Distance (Å)		
S1	NI[a]	NI[*]	Tyr211, Pro262, Ile323, Ile363, Val380, Phe416	−7.5
S2	Tyr211	3.10	Tyr211, Ile323, Ile363, Val380, Phe384, Phe416	−8.9
	Asn365	2.72		
S3	Tyr211	3.03	Ile323, Ile363, Val380, Phe384, Phe416	−8.5
S4	Asn260	3.16	Tyr211, Ile323, Val380, Phe416	−8.6
S5	Gln413	3.15	Tyr211, His216, Val380, Phe416	−8.8
S6	Gln413	2.96, 3.22	Tyr211, His 212, His216, Ile323, Val380, Phe416	−9.5
Control[b]	Gln413	3.34	Tyr211, His216, Ile323, Val380, Phe416	−7.9

[a]No significant interaction with binding site residues.

[b]Control: Co-crystallized PDE7 inhibitor (2-(cyclopentylamino)-3-ethyl-7-ethynylthieno[3,2-d]pyrimidin-4(3H)-one) (PDB ID: 4PM0).

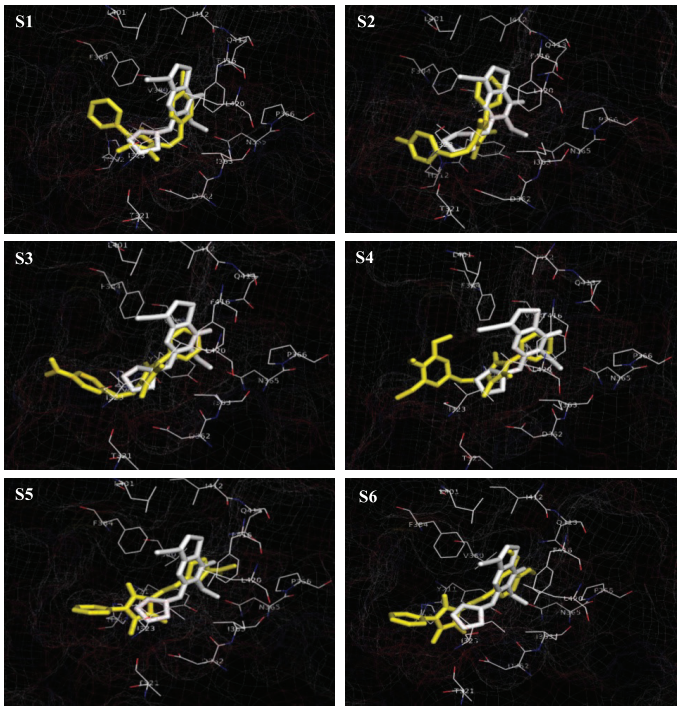


Figure 2. Orientation and overlay of the docked poses of the synthesized compounds (S1–S6) (yellow sticks) with that of PDB ligand 4PM0 (white sticks) in the binding site of PDE7.

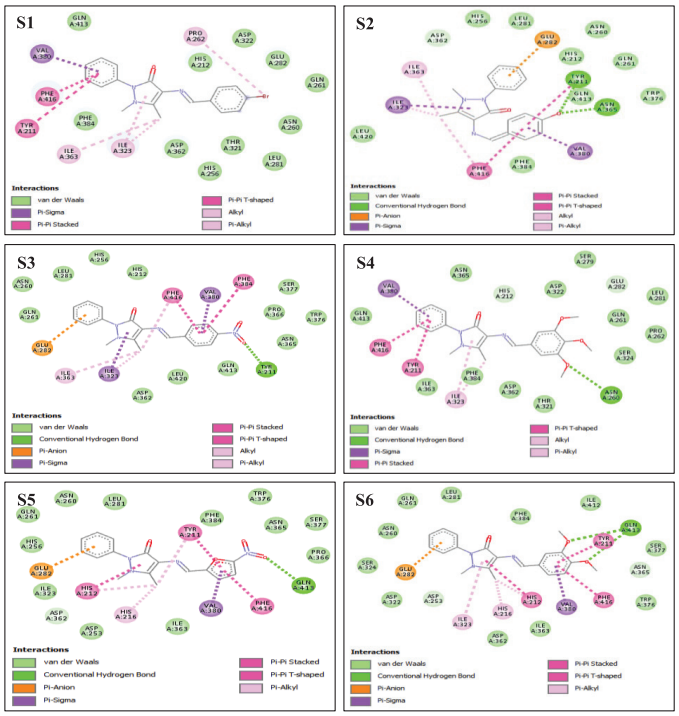


Figure 3. Docked poses showing various types of binding interactions, including H-bond and hydrophobic interactions of the synthesized compounds (S1–S6) with the binding site residues of PDE7 protein.

3-one" ring of S2 showed hydrophobic interactions with Ile323 and Ile363 residues in the binding site of PDE7. S3 showed one H-bond with Tyr211 residue of PDE7 enzyme with bond length of 3.03 Å. S4 formed one H-bond with Asn260 residue of PDE7 enzyme with bond length of 3.16 Å. Compound S5 showed one H-bond Gln413 residue of PDE7 enzyme with bond length of 3.15 Å. S6 showed two H-bond interactions between -O- group and NH group of Gln413 residue of PDE7 protein with bond length of 2.96 and 3.22 Å, respectively. The "3,4-dimethoxyphenyl" ring of S6 protruded in hydrophobic pocket showing interactions with Tyr211, Val380, and Phe416 residues in binding site of PDE7. The "1,2-dihydropyrazol-3-one" ring of S6 showed hydrophobic interactions with His212, His216, and Ile323 residues and "phenyl" ring showed hydrophobic interactions with Glu282 residue (Figure 3). Thus, molecular docking studies carried out on the synthesized molecules helped us in predicting that these compounds possess stable and significant H-bonds and hydrophobic interactions with PDE7 protein, expecting that these synthesized molecules could act as potent inhibitors of PDE7.

CONCLUSION

Schiff bases of 4-aminopyrazone have a deep impact in medicinal chemistry. Since many years, these bases have been synthesized and have been evaluated for various pharmacological activities against a wide range of targets. This research paper mentions the synthesis of Schiff bases by an efficient methods, i.e., grinding technique, which were characterized on the basis of melting point, FTIR, and NMR spectroscopy. All the synthesized molecules showed appreciable docking interactions with binding site residues of the PDE7 protein and good ADME properties for oral bioavalability.

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Author Contributions: All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

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