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Design Synthesis And Biological Evaluation Of Pyrazolyl-Thiazole Incorporated Coumarinyl Pharmacophore And Docking Studies

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Abstract

A novel series of substituted pyrazolyl-thiazole incorporated with coumarinyl pharmacaphore were designed and synthesized. The structure of title compounds were characterized by spectroscopic data IR, NMR, mass spectral data and elemental analysis. The compounds were evaluated for their anti-diabetic activity against Acarbose cell line and anti oxidant activity against pathogenic microbial strains. Molecular docking is the in silico technique which is used to extend the homology model for the new drug candidate. This field will reduce the number of synthetic compound in drug discovery research. The synthesized pyrazolyl-thiazole compounds showed a very good anti-diabetic activity. Thus, we continued to dock the ligand with enzyme like alpha amylase. Here, the synthesized compounds were docked with 2HR7 enzymes with the use molecular docking tools and the docking results are briefly explained. The various types of interactions amidst the compounds and amino acid residue of enzyme were reported.

Keywords: *Thiazole, Pyrazole, Antioxidant activity, Antidiabetic, Acarbose, Molecular docking.*

1. Introduction

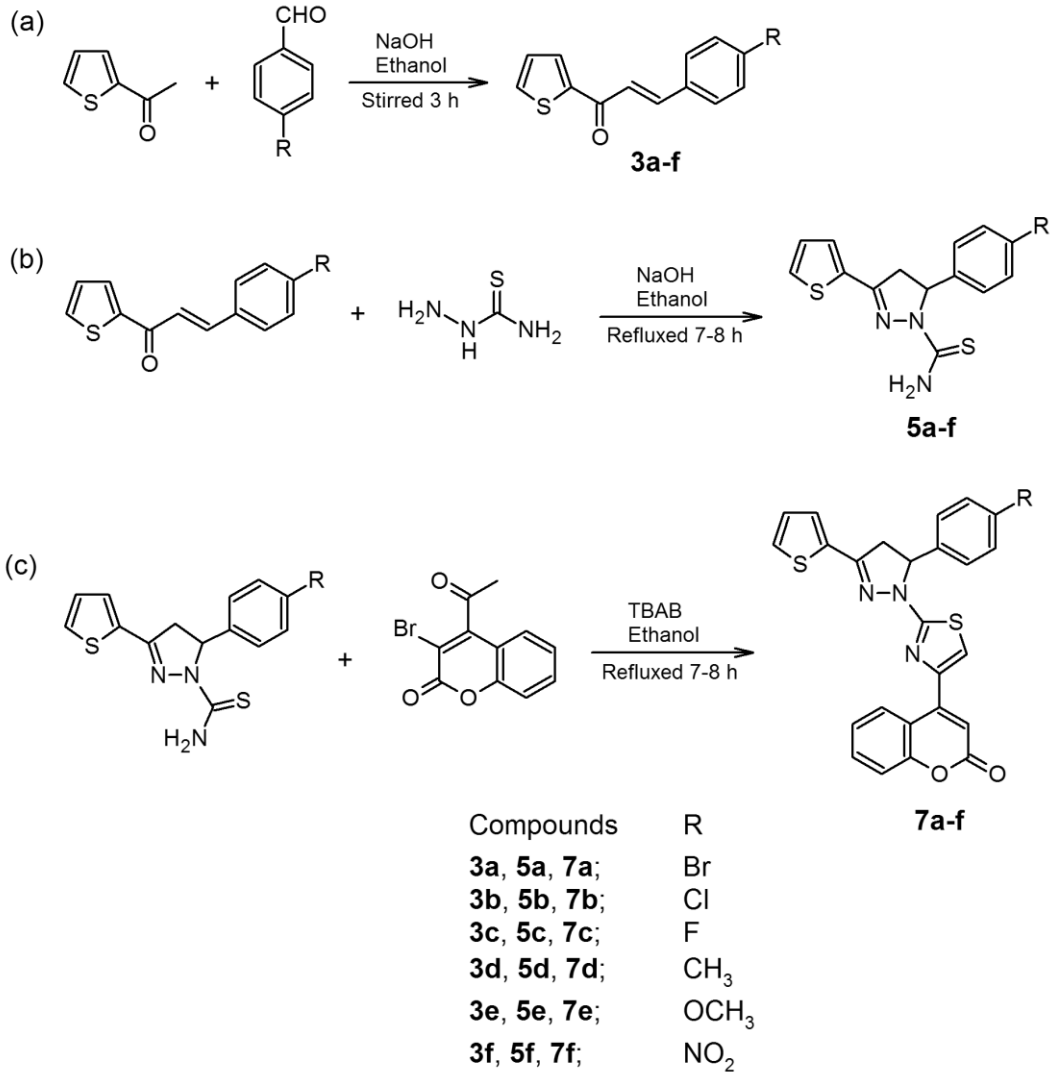
Heterocyclic compounds are common in different fields of life sciences. These compounds bring out several extensive tasks in technology, nature and medicine. Heterocyclic hybrids have become most promising molecules due to its a range of potential as novel drug an diabetes in recent drug discovery. It is a daring and vital issue for the pharmaceutical industry and scholastic researchers to develop new drugs and pharmaceuticals [1]. The pyrazoles are important parts of many heterocyclic compounds. They have extensive workspace due to biologic activities and medicinal properties [2]. Thiazole is also used in the synthesis and applications of bio mimicking and bioactive coordination compounds due to the flexible coordination capacity of nitrogen and sulfur atoms toward various transition metal ions [3]. Along with the methods of oxidization protection, using inhibitors is a common and important method. Between organic compounds, aromatic heterocyclic compounds containing N, S, O and π-electrons have high prospective to be considered as corrosion inhibitors [4–5]. The biological activity of substituted thiazoles were have (S–C=N) toxophoric unit [6]. Representative examples of this group of compounds were informed to prove anticancer [7], antibacterial [8], antifungal [9] and antioxidant activities [10]. In addition, natural and synthetic molecules consisting thiazole scaffold participate a significant role in pharmaceutical industry due to their anti-inflammatory [11], anti-HIV [12] properties. The antibiotic drugs - penicillin, antitumor agent and Bleomycin [13–14] contain thiazole motif. In addition, a few thiazole-containing compounds have physical applications, for example, thiophene-thiazole functionalized conjugated oligomers have been used for the fluorescent and colorimetric sensing of Cu^{2+} and Fe^{2+} from water and thiazole-based iridium(III) complexes for organic light-emitting diode (OLED) applications [15]. Furthermore, several thiazole derivatives have been effectively occupied in a variety of fields of organic chemistry, agriculture and medicines, and have also been considered as functional intermediates for synthetic drugs, dyes and fungicides. On the other hand, coumarin derivatives are known to cover range of biological activities, including anti-HIV, anti-acetyl cholinesterase, antifungal, antioxidant, anti-helmintic, antitumor, antibacterial, antiviral, and anticlotting activities, and find extensive application in pharmaceuticals, fragrances, agrochemicals, live cell imaging and as additives in food, cosmetics [16]. All the synthesized compounds were evaluated for their α-amylase and α-glucosidase inhibitory activity. α-Amylase and α-glucosidase are the enzymes that convert disaccharides and oligosaccharides into monosaccharide. Acarbose, miglitol and voglibose are the drug generally used to inhibit these enzymes to prevent the absorption of glucose [17]. The antioxidant activity (AOA) of thiazole derivatives has been acknowledged recently. We used two *in vitro* tests that make use of different principles of red-ox reactions are 1,1-diphenyl-2-picrylhydrazyl scavenging capacity test, i.e. DPPH radical scavenging

capacity (or DPPH) and nitric oxide (NO) assay [18]. So the molecule as a whole has to be taken in to consideration. Keeping in view of this and in continuation of our search on biologically potent molecules we planned to synthesis new series pyrazolyl-thiazolyl coumarin hybrids possessing a wide spectrum of biological activities. Additionally, our objective is also to study the anti-diabetic, antioxidant and anti-microbial activities of the synthesized compounds. Unique bioactivities of some compounds can be illuminated by interaction between the compounds and the target protein. Therefore to achieve effective drug design molecular docking studies for the compounds to be synthesized is also carried out.

2. Results and discussion

2.1. Chemistry

The synthesis of the targets has been achieved in three steps as shown in Scheme 1. 2-acetyl thiophene was condensed with substituted benzaldehyde in basic condition to afford the chalcone (3a-f). chalcone (3a-f) on further treatment with thiosemicarbazide in the presence of sodium hydroxide yielded the corresponding pyrazole (5a–f) derivatives. Further, the study demonstrates here the novel in situ method for the heterocyclization of the thiosemicarbazone(5a-f) into a thiazole ring upon treatment with 3-bromoacetyl coumarin in under reflux condition tetrabutylammonium bromide (TBAB) used as a catalyst. In the IR spectrum of 7a–f the stretching frequency at 1174 cm–1 is due to C–S, the sharp peak at 1588 cm–1 is due to C=N. The stretching frequency observed at 1708 cm–1 is assigned to the coumarinyl (C=O). High-resolution ^{1}H and ^{13}C NMR have been recorded in $CDCl_3$ and analyzed. In the ^{1}H NMR spectrum of 7a, the doublet at 3.92 ppm is due to methylene proton, the triplet at 5.02 ppm is due to methine proton, and the signal at 6.72 ppm is assigned to the methine proton in the thiazole ring. The signals appearing at 6.23–7.81 ppm are obviously due to aromatic protons. In the ^{13}C NMR spectrum of 7a the signal at 59.82 ppm is due to methine carbon, the signal observed at 111.01 ppm is due to the C–S carbon. The signal at 167.43 ppm is assigned to C=N carbon. The signal appeared at 173.41 ppm is due to C=O carbon. The signals in the region 121.73–154.87 ppm is due to aromatic carbons. The peak observed at 499.14 ppm is the mass spectrum of 7a is the consistent with the molecular mass of the system.



Scheme 1. Synthesis of compounds a) **3a–f**, b) **5a–f** and c) **7a–f**.

2.2. Biological review

2.2.1. Antioxidant screening

2.2.1.1. Determination of DPPH radical scavenging activity.

Scavenging activities were estimated by means of the technique followed by Braca et al. [19]. The antioxidant screening results (Table 1) depicted that all the tested compounds displayed variable antioxidant activity against DPPH with respect to ascorbic acid. The results showed that compound **7a** exhibited strong antioxidant activity against the DPPH radicals with IC_{50} of 10.38 μg/mL, relative to asorbic acid having IC_{50} value of 23.13 μg/mL. In addition, compounds **7b** and **7c** exhibited good DPPH free radical scavenging potential with IC_{50} value 23.08 and 22.63 μg/mL higher than that of the standard ascorbic acid with IC_{50} value of 23.13 μg/mL. Compounds **7d**, **7e** and **7f** showed modest antioxidant activity with IC_{50} values ranging from 63.41 to 85.02μg/mL (Fig. 1a) correspondingly.

2.2.1.2. Determination of nitric oxide radical scavenging activity. Analysis of the capability of the tested compounds to scavenge nitric oxide (NO) free confides was resolved by means of the technique announced by Ho et al. [20]. This technique relies upon the generation of nitric oxide from sodium nitroprusside arrangement at physiological pH that responds with oxygen to give nitrite particles that can be dictated by utilizing Gries reagent. The results listed in Table 1 revealed that compounds **7a**, **7b** and **7f** are stronger antioxidants with IC_{50} values of 11.08, 22.85 and 18.23 μg/mL, respectively,

than the standard ascorbic acid with IC_{50} value of 42.03 μg/mL. Compounds **7c**, **7d** and **7e** were nearly equipotent to the standard ascorbic acid with IC_{50} values of 49.12, 63.08 and 79.72 μg/mL (Fig. 1b), respectively.

Table 1
Results of *in vitro* antioxidant activity of **7a–f** using DPPH and NO.

Compound	IC_{50} (μg/mL)	
	DPPH	NO
7a	10.38	11.08
7b	23.08	22.85
7c	22.63	49.12
7d	63.41	63.08
7e	52.02	79.72
7f	85.02	18.23
Ascorbic acid	23.13	42.03

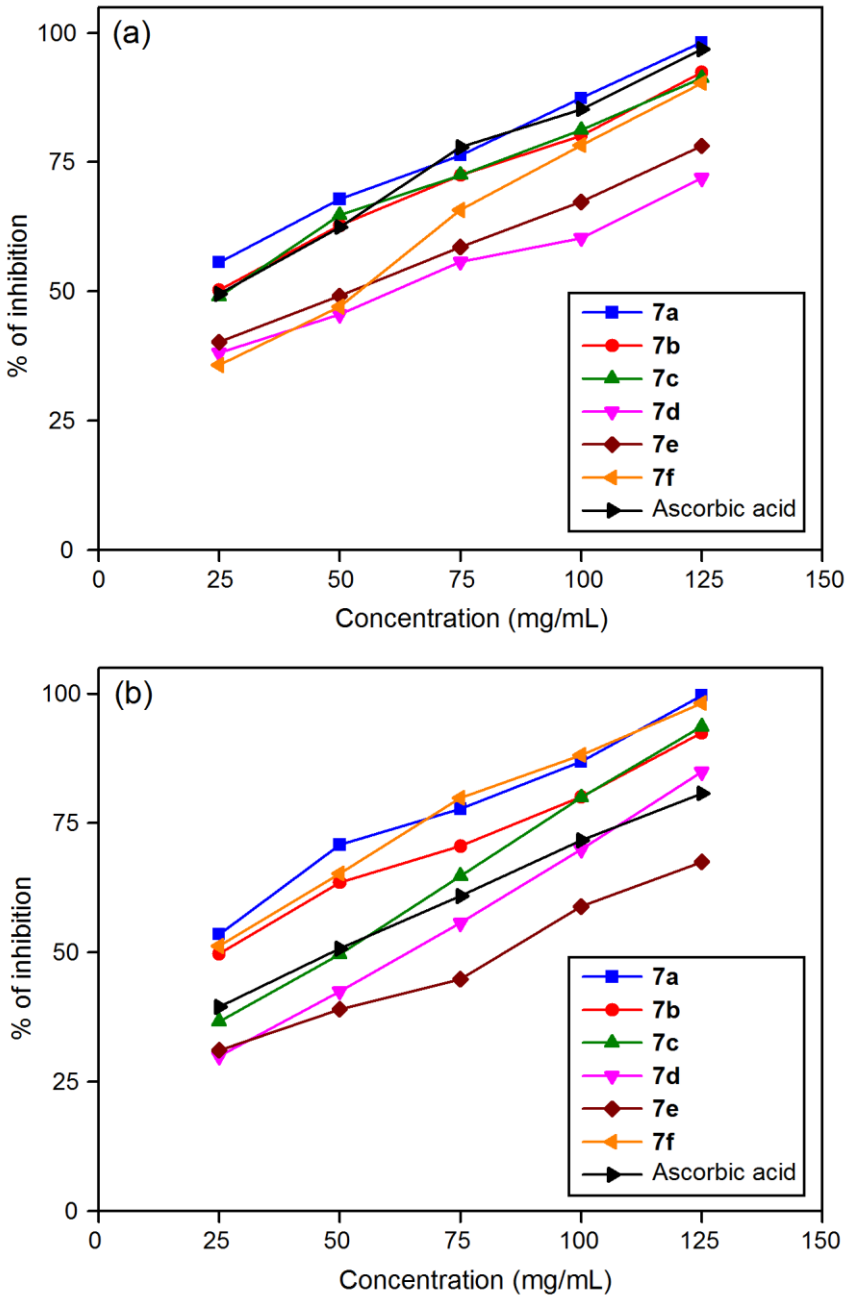


Fig. 1. Antioxidant activity results using a) DPPH and b) NO.

2.2.2. In vitro antidiabetic assay

2.2.2.1. α-Amylase inhibitory activity. α-Amylase inhibitory activity of substituted thiazole compounds was carried out according to the standard method with minor modification [21]. All the synthesized compounds were tested for their α-amylase activity. It was observed substituted thiazoles **7a**–**7f** showed more potent α-amylase inhibitory action as compared to benzylated derivatives. Among the derivatives, it was observed that compounds **7a** and **7b** were found the highest active inhibitors of α-amylase enzyme at different extents and IC_{50} values 10.49, 17.09 µg/mL the results listed in Table 2. Both of them were found better than Acarbose, which was having IC_{50} 18.23 µg/mL. Log concentrations *versus* percentage inhibition curves were plotted and IC_{50} values were calculated for all compounds (Fig. 2a). Among these, **7c** has shown the maximum activity against α-amylase with IC_{50} 20.41 µg/mL whereas **7f** was the lowest potent α-amylase inhibitor with IC_{50} 50.52 µg/mL.

2.2.2.2. α-Glucosidase inhibitory activity.

The synthesized substituted thiazoles (**7a–f**) were evaluated for *in vitro* antihyperglycemic activity study against α-glucosidase enzymes. The % inhibition results are represented in Table 2. It was established that all the compounds were shown in Fig. 2b, the gradual increase of inhibition as the concentration of the sample increased. From the results, it was found compounds **7a**, **7b** and **7c** bearing bromo, chloro, and fluoro substituent on the phenyl ring of the thiazole moiety have shown stronger inhibition with IC_{50} values are 11.44, 15.33 and 15.98 μg/mL, respectively than Acarbose 17.23 μg/mL. Compound **7f** showed mild inhibitory activity against nitric oxide free radical scavenging activity with IC_{50} value of 47.57 μg/mL.

Table 2

Results of *in vitro* antidiabetic activity using α-amylase and α-glucosidase.

Compound	IC_{50} (μg/mL)	
	α-Amylase	α-Glucosidase
7a	10.49	11.44
7b	17.09	15.33
7c	20.41	15.98
7d	22.51	24.43
7e	46.46	42.99
7f	50.52	47.57
Acarbose	18.23	17.23

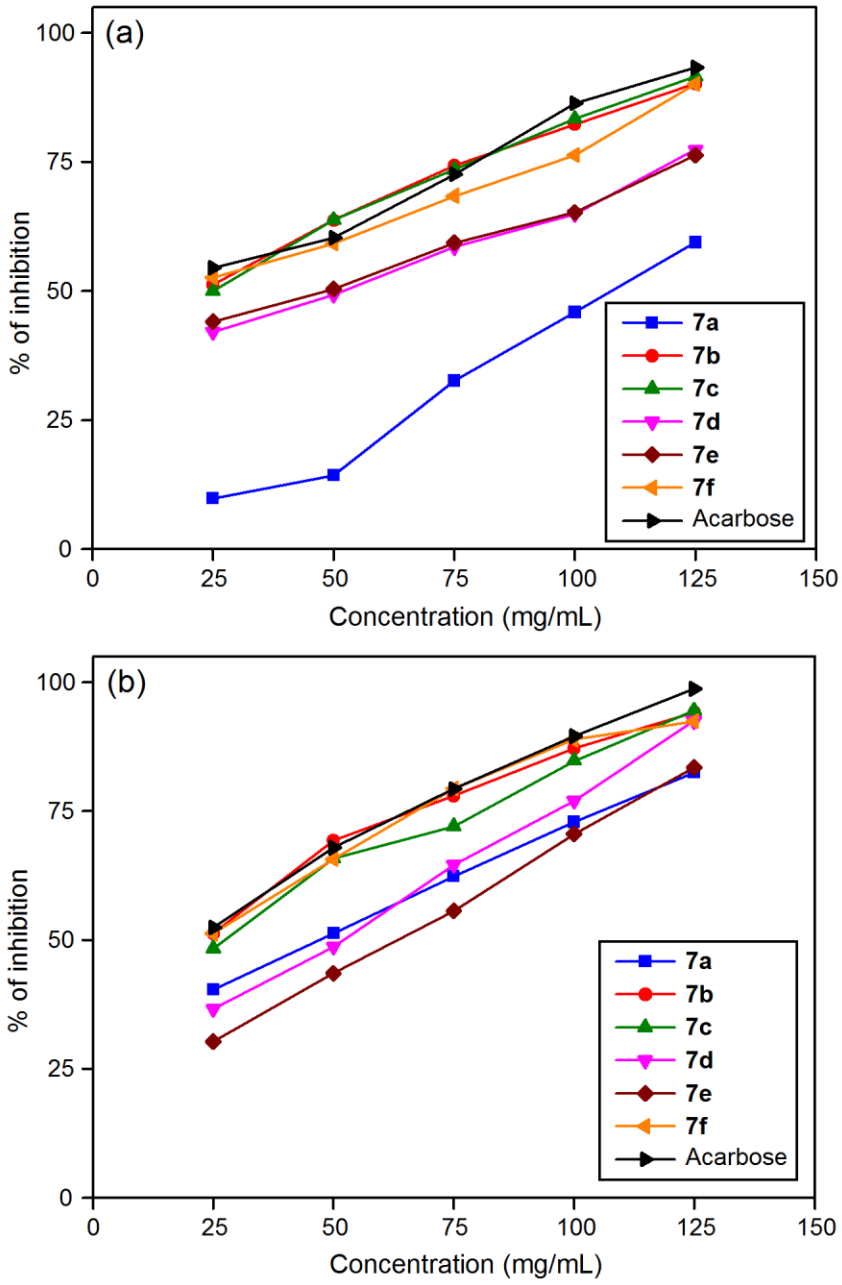


Fig. 2. Antidiabetic activity results using a) α-amylase and b) α-glucosidase.

2.2.3. Molecular docking studies

Molecular docking studies are increasing attention in current research because it is one of the most important computer design programs that help to find out the major interaction of the ligand in the active pockets of the target [22]. All the newly synthesized compounds are chosen for molecular docking studies. The Schordinger 9.0 docking method is used to determine the orientation of the ligands bound in the active site of anti-diabetic target protein (receptor) 2HR7. The synthesized compound and standard drug (Acarbose) were docked into antidiabetic affinity. Docking study was carried out by using molecular operating environment (MOE) software package. The docking results showed that all compounds were well accommodated in the binding pocket of α-glucosidase. The molecular docking interactions are listed in Table 3. The docking conformation of most active compound **7a** (IC_{50} = 10.49 μg/mL) with bromine group at *para* position of phenyl ring showed good interaction

network as well as good docking score (–6.901 kcal/mol). Compound **7a** made three π-interactions at the binding pocket. PHE64made interaction with bromobenzene group and PHE88 with thiazole ring. Additionally PHE96 interact with coumarinyl ring. Furthermore, compounds **7b** and **7c** demonstrated ARG118, PHE96 formed interaction with chlorobenzene and fluorobenzene ring. The docking score was –5.450 and –5.231 kcal/mol. Observation of the binding interactions of compound **7d** between the oxygen atom of the coumarinyl ring and the amino acid GLN34 and the docking score –5.204 kcal/mol. Similarly ARG118, PHE96 interact with methylbenzene ring. Compound **7e** docking score is –5.053 kcal/mol and made PHE96 interact with methoxybenzene ring. Finally, compound **7f** exhibited hydrogen bond between the thiazole ring and PHE88 and the PHE96 made two interactions with coumarinyl ring and the docking score was –4.693 kcal/mol.

Table 3

Molecular docking results for the tested compounds and redocked ligand during docking enzyme Acarbose (PDB: 2HR7)

Compound	Docking score (kcal/mol)	Number of hydrogen bonds	Interacting residues of 2HR7
7a	–6.901	3	PHE64, PHE88, PHE96
7b	–5.450	2	PHE96, ARG118
7c	–5.231	3	GLN34, PHE96, ARG118
7d	–5.204	3	GLN34, PHE96, ARG118
7e	–5.053	2	GLN34, PHE88
7f	–4.693	2	PHE88, PHE96

3. Experimental

*3.1. General procedure for 3-(4-chlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3a–f**)*

To a suspension of appropriate (**1a–f**) (0.1 mmol) and substituted benzaldehyde (0.1 mmol) in ethanol was stirred for 3–6 h in the presence of 10% NaOH. The reaction mixture was poured into water. The solution was cooled and the product was filtered and recrystallized using ethanol.

*3.2. General procedure for 5-(4-chlorophenyl)-4,5-dihydro-3-(thiophen-2-yl)pyrazole-1-carbothioamide (**5a–f**)*

To a suspension of **3a–f** (0.1 mmol) is refluxed with thiosemicarbazide (0.1 mmol) for 9 h in presence of ethanolic NaOH. The reaction mixture was poured into water and the precipitate obtained was filtered, washed and recrystallized from ethanol.

*3.3. General procedure for 4-(2-(5-(4-chlorophenyl)-4,5-dihydro-3-(thiophen-2-yl)pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**7a–f**)*

A mixture of **5a–f** (0.1 mmol) and the 3-(bromoacetyl)coumarin (0.1 mmol) in ethanol and refluxed for 8 h using tetrabutylammonium bromide (TBAB) as catalyst. The mixture was allowed to cool at room temperature. The separated solid was filtered, air-dried and recrystallized from ethanol.

*3.3.1. 4-(2-(5-(4-Bromophenyl)-4,5-dihydro-3-(thiophen-2-yl)pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**7a**)*

Yield 60%; m.p. 230–233 °C; yellow solid. IR (KBr, ν cm^{-1}): 1602 (C=N), 3052 (ArC–H), 755 (C–S), 1716 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.0 (d, 2H), 3.9 (t, 1H), 6.6 (s, 1H, CH thiazole), 6.48 (s, 1H), 7.0–7.38 ArH (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 40.7, 53.1, 113.2, 121.5, 125.2, 125.4, 126.8, 127.1, 126.9, 128.4, 129.2, 136.4, 139.3, 140.5, 158.1, 160.3, 167.4. Anal. Calcd. (%) for $C_{25}H_{16}BrN_3O_2S_2$: C, 56.18; H, 3.02; Br, 14.95; N, 7.86; O, 5.99; S, 12.00.

*3.3.2. 4-(2-(5-(4-Chlorophenyl)-4,5-dihydro-3-(thiophen-2-yl)pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**7b**)*

Yield 62%; m.p. 191–194 °C; white solid. IR (KBr, ν cm^{-1}): 1608 (C=N), 2990 (ArC–H), 808 (C–S), 1710 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.35 (s, 1H), 1.7 (d, 2H), 3.5 (t, 1H), 6.8 (s, 1H, CH thiazole), 7.0–7.38 ArH (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 24.3, 41.8, 54.3, 114.2, 120.3, 127.2, 128.4, 129.8, 130.1, 131.4, 132.4, 133.2, 135.4, 137.3, 138.5, 154.1, 162.3, 169.4. Anal. Calcd. (%) for $C_{25}H_{16}ClN_3O_2S_2$: C, 61.28; H, 3.29; Cl, 7.24; N, 8.58; O, 6.53; S, 13.09.

*3.3.3. 4-(2-(5-(4-fluorophenyl)-4,5-dihydro-3-(thiophen-2-yl)pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**7c**)*

Yield 60%; m.p. 270–273 °C; pale white solid. IR (KBr, ν cm^{-1}): 1612 (C=N), 3056 (ArC–H), 759 (C–S), 1702 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.4 (d, 2H), 3.6 (t, 1H), 6.5 (s, 1H, CH thiazole), 7.0–7.38 ArH (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 42.7, 51.1, 111.4, 123.6, 126.3, 127.4, 128.7, 129.3, 130.9, 131.4, 132.2, 134.4, 136.3, 145.5, 158.1, 160.3, 180.4. Anal. Calcd. (%) for $C_{25}H_{16}FN_3O_2S_2$: C, 63.41; H, 3.41; F, 4.01; N, 8.87; O, 6.76; S, 13.54.

*3.3.4. 4-(2-(4,5-Dihydro-3-(thiophen-2-yl)-5-p-tolylpyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**7d**)*

Yield 60%; m.p. 195–198 °C; yellow solid. IR (KBr, ν cm^{-1}): 1613 (C=N), 3021 (ArC–H), 810 (C–S), 1716 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.73 (s, 3H), 1.9 (d, 2H), 3.3 (t, 1H), 6.4 (s, 1H, CH thiazole), 6.7–7.38 ArH (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 40.7, 53.1, 55.9, 110.7, 121.5, 125.2, 125.4, 126.8, 127.1, 126.9, 128.4, 129.2, 136.4, 139.3, 140.5, 156.1, 163.3, 173.4. Anal. Calcd. (%) for $C_{23}H_{16}N_3O_2S_2$: C, 66.50; H, 4.08; N, 8.95; O, 6.81; S, 13.66.

*3.3.5. 4-(2-(4,5-Dihydro-5-(4-methoxyphenyl)-3-(thiophen-2-yl)pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**7e**)*

Yield 60%; m.p. 171–174 °C; dirty white solid. IR (KBr, ν cm^{-1}): 1610 (C=N), 3021 (ArC–H), 774 (C–S), 1698 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.81 (s, 3H), 2.1 (d, 2H), 3.4 (t, 1H), 6.5 (s, 1H, CH thiazole), 6.7–7.38 ArH (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 41.7, 51.1, 58.29, 114.7, 123.5, 124.3, 126.2, 126.8, 127.1, 126.9, 128.4, 129.2, 136.4, 139.3, 140.5, 156.1, 163.3, 173.4. Anal. Calcd. (%) for $C_{26}H_{19}N_3O_3S_2$: C, 64.31; H, 3.94; N, 8.65; O, 9.88; S, 13.21.

*3.3.6. 4-(2-(4,5-Dihydro-5-(4-nitrophenyl)-3-(thiophen-2-yl)pyrazol-1-yl)thiazol-4-yl)-2H-chromen-2-one (**7f**)*

Yield 60%; m.p. 197–200 °C; white solid. IR (KBr, ν cm^{-1}): 1610 (C=N), 2998 (ArC–H), 821 (C–S), 1711 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.3 (d, 2H), 3.6 (t, 1H), 6.1 (s, 1H, CH thiazole), 6.9–7.48 ArH (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 44.4, 55.1, 110.2, 123.5, 126.2, 127.4, 128.8, 129.1, 130.9, 131.4, 132.2, 133.4, 135.3, 143.5, 157.1, 162.3, 164.4. Anal. Calcd. (%) for $C_{25}H_{16}N_4O_4S_2$: C, 59.99; H, 3.22; N, 11.19; O, 12.79; S, 12.81.

4. Conclusion

In summary we have developed a novel and convenient method for the synthesis of a series of heterocyclic compounds possessing biologically potent pyrazolyl-thiazole nucleus with good to excellent yield and purity and determined with different spectroscopic techniques. The new compounds were investigated for inhibition against α-amylase and α-glucosidase and antioxidant activities. Molecular modeling environment (MOE) evaluated the binding free energies of these inhibitors into the target α-amylase receptor. It was found that the MOE were typically concise with the experimental data.

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