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Synthesis and antitumor activity evaluation of some N-heterocycles derived from pyrazolyl-substituted 2(3*H*)-furanone

Wael S. I. Abou-Elmagd[1], Ahmed K. EL-Ziaty[1], Magdy I. Elzahar[2], Sayed K. Ramadan[1], Ahmed I. Hashem[1]

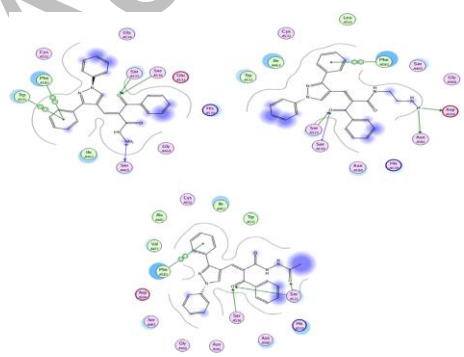
[1]Chemistry Department, Faculty of Science, Ain Shams University, Abassia, Cairo, Egypt [2]Therapeutic chemistry department, National Research Center, Dokki, Cairo, Egypt

Corresponding should be addressed E-mail: waelmagd97@yahoo.com

Abstract

Pyrazolyl-substituted 2(3*H*)-furanone was allowed to react with different nitrogen nucleophiles such as hydrazine hydrate, ethylenediamine, ethanolamine and anthranilic acid to give pyrrolone and benzoxazinone derivatives. The acid hydrazide **3** was reacted with some carbonyl compounds such as 4-chlorobenzaldehyde, chloroacetyl chloride and acetic anhydride to give thiazolidinone, oxadiazole, pyridazinone derivatives. Selected examples of the synthesized compounds were evaluatedas anticancer agents against three types of carcinoma cell lines (HePG 2, HCT116 and PC3), using *Doxorubicin* as a reference drug. The result revealed that some of the new compounds showed high activities. Compound **6a** was more potent than the standard drug. Docking study using MOE 2008.10 program was performed.

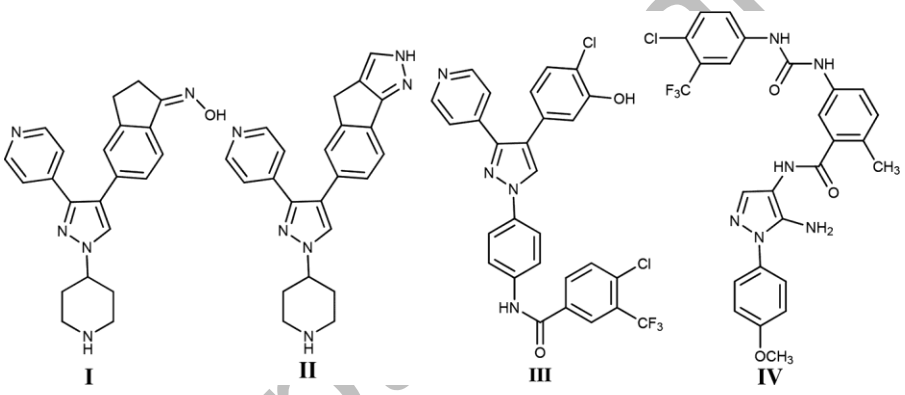
Graphical Abstract



KEYWORDS: 2(3*H*)-furanone, pyrazole, pyrrolones, thiazolidinones, Antitumor activities

INTRODUCTION

There is a variety of N-heterocycles bearing pyrazole derivatives developed as a new scaffold of antitumor agents. All are effective against lungs cell carcinoma (A549) and also showed anti-proliferative activity against human lung cancer cell lines and inhibited tubular polymerization.[1-14] Also, it has been documented that different newly designed and synthesized pyrazolyl derivatives showed anticancer activity due to their B-Raf inhibitory activities with IC50 values in the nano levels as compounds I, II, III, IV.[15-18]



The utilization of 2(3*H*)-furanones for the construction of a wide variety of nitrogenous heterocyclic ring systems of synthetic and biological importance had been a subject of research concern by our research group.[1,19-32] These diverse biological activities initiated our interest in utilizing the 2(3*H*)-furanone **1** bearing a pyrazolyl moiety as side chain for the synthesis of nitrogen containing heterocycles of anticipated antitumor activities.

RESULTS AND DISCUSSION

Synthesis

The 2(3*H*)-furanone **1** was previously prepared by our research group.[19] Fusion of the furanone **1** with ammonium acetate in a sand bath at 150^0C gave the pyrrolone derivative **2**. The structure of **2** is substantiated from its spectral data. The IR spectrum shows disappearance of absorption of the lactone C=O group and the appearance of absorption band of C=O group for the cyclic amide at 1699cm^{-1}(cf. experimental part). Treatment of **1** with other nitrogen nucleophiles such as hydrazine hydrate, benzyl amine, anthranilic acid ethanolamine and ethylenediamine led to the formation of a wide variety of N-heterocycles (Scheme 1). Thus, refluxing **2** with hydrazine hydrate and benzylamine in ethanol gave the acid hydrazide and N-benzylamide derivatives **3** and **4** respectively**.** The structures of **3** and **4** were illustrated from their spectral data and supported by comparison with an authentic sample prepared by treatment of furanone **1** with hydrazine hydrate and benzylamine respectively.[16] Treatment of the 2(3*H*)-furanone **1** with anthranilic acid in acetic acid in the presence of anhydrous sodium acetate gave the benzoxazinone derivative **5.** The structure of **5** was elucidated from its analytical and spectral data (cf. experimental part). The IR spectrum showed disappearance of absorption of C=O group of the 2(3*H*)-furanone and the appearance of absorption peaks for C=O group of benzoxazinone at 1744 cm^{-1} (cf. experimental part). The assigned structure is supported by ^{1}H-NMR and mass spectra. The MS spectrum showed the correct molecular ion peak beside some of abundant peaks (cf. experimental part).

Stirring of **1** with ethanolamine or ethylenediamine in ethanol at room temperature afforded the amide derivative **6a** or **6b** respectively. Heating the amide derivative **6a** in

n-butanol gave the pyrrolone derivative **7**. The structures of **6** and **7** were confirmed from their analytical and spectral data (cf. experimental part). On the other hand, refluxing **1** was ethylenediamine in ethanol/ acetic mixture gave the dipyrrolonyl derivatives **8.** Compound **8** was also obtained by refluxing the pyrrolone **7** with the furanone **1** under the same reaction conditions. The structures of compounds **6-8** were substantiated from their spectral and analytical data (cf. experimental part).

The acid hydrazide derivative **3** was treated with some carbonyl compounds to give oxadiazole, pyridazinone and thiazolidinone derivatives. Thus, when **3** was heated with 4-chlorobenzaldehyde in ethanol, it gave the Schiff base **9**. However, the oxadiazole derivative **10** was obtained when the reaction was carried in dioxane. The mechanistic pathway for the formation of the oxadiazole derivative **10** is represented in (Scheme 2).

The Schiff base **9** was easily converted into the thiazolidinone derivative **11** when treated with thioglycolic acid. On the other hand, chloroacetyl chloride reacted with the acid hydrazide derivative **3** to give the corresponding pyrrolone derivative **12**. Acetic anhydride was allowed to react with the acid hydrazide **3** under two reaction conditions. Stirring **3** with acetic anhydride at room temperature gave the diamide derivative **13**. Ring closure of **13** using HCl/AcOH mixture gave the pyridazinone derivative **15**. However, the oxadiazole derivative **14** was obtained by refluxing **3** with acetic anhydride. The thiosemicarbazide derivative **16** was obtained by treating **3** with phenyl isothiocyanate. Treatment of **16** with ethyl bromoacetate and maleic anhydride gave the

thiazolidinone derivatives **17** and **18** respectively. The mechanistic pathway for the formation of the thiazolidinone derivatives **18** is represented in (Scheme 3).

The structures of compounds **9–18** were confirmed by the analytical and spectroscopic data. The assigned structures were strongly confirmed from ^{1}H-NMR and mass spectra (cf. experimental part). All the foregoing reactions are illustrated by (Scheme 4).

Evaluation Of The Antitumor Activity

Cytotoxic Effect On Human Cell Lines (Hepg 2, HCT116 And PC3)

The pyrazolyl derivatives were examined as anticancer agents against three types of carcinoma cell lines, Human liver carcinoma (HePG 2), Human colon carcinoma (HCT116) and Human prostate cancer (PC3) cell lines, using *Doxorubicin* as a reference drug. As a trial to get more effective and less toxic agents, only four compounds (**3, 6a, 12, 13**) exhibited the desired activity. The biological results showed that the most potent activity was gained upon conjugation of the parent pyrazole heterocycle with amidic long chain functionality (compound **6a**). The obtained activity was higher than that obtained by the reference drug against the three examined carcinoma cell lines (IC50; 6.25-12.40 µg/ml, $IC50_{Dox}$; 21.6-37.6 µg/ml) (cf. Tables part).

The reduction in the length of the amidic side chain to form the pyrazolohydrazide derivative **3** retains the anticancer potency against HCT116 and PC3, that is higher than that of *Doxorubicin* (IC50; 14.1, 11.6 µg/ml), while the activity decreased against HePG 2 cell lines to be less than the reference drug (IC50; 49.0 µg/ml).

On the other hand, the attachment of two amide groups at pyrazole-C4 (compound **13**) produced a noticeable reduction in the activity against HCT116 carcinoma cell lines (IC50; 70.5 µg/ml) and abolishes the activity completely against PC3 cell lines, but retains the potent anticancer activity against HePG 2 (IC50; 13.9 µg/ml). Cyclization of the side chain at pyrazole-C4 to form the pyrrole-acetamide nucleus (compound **12**) led to further decrease in the potency against the examined cancer cell lines (IC50; 46.3-76.1 µg/ml).

Molecular Modeling Studies

All the molecular modeling calculations and docking simulation studies were performed using Molecular Operating Environment (MOE®) 2008.10.[33] All the interaction energies and different calculations were automatically calculated.

The target compounds were constructed into a 3D model using the builder interface of the MOE program. After checking their structures and the formal charges on atoms by 2D depiction, the following steps were carried out: the target compounds were subjected to a conformational search. All conformers were subjected to energy minimization, all the minimizations were performed with MOE until a RMSD gradient of 0.01 Kcal/mole and RMS distance of 0.1 Å with MMFF94X force-field and the partial charges were automatically calculated. The obtained data base was then saved as MDB file to be used in the docking calculations.

The origin of the selectivity of (1*E*)-5-(1-piperidin-4-yl-3-pyridin-4-yl-1*H*- pyrazol-4-yl)-2,3-dihydro-1*H*-inden-1-one oxime),SM5 (I) for B-Raf seems to be due to interactions with several B-Raf amino acids, as well as the presence of the indane-oxime. In particular, a Phe583 in the COOH-terminal lobe of B-Raf forms favorable π-stacking interactions with the pyrazole and pyridine rings of SM5 (I). Furthermore, a Trp531 is located above the opposing face of the pyridine, forming favorable π-stacking interactions. Additionally, the hydroxyl group of indane-oxime forms two strong hydrogen bonds with Lys 483 and Glu501, thus likely contributing to the selectivity and potency of SM5 (I). (Fig. 1).

The X-ray crystallographic structure of B-Raf receptor complexes with SM5 (PDB ID: 3D4Q) was obtained from the Protein Data Bank through the internet. The enzyme was prepared for docking studies by removing the ligand molecule, SM5 from B-Raf receptor active sites. Hydrogen atoms were added to the system with their standard geometry. The atoms connection and type were checked for any errors with automatic correction. Selection of the receptor and its atoms potential were fixed. MOE Alpha Site Finder was used for the active site search in the enzyme structure using all default items. Dummy atoms were created from the obtained alpha Spheres. Re-docking of co-crystalline ligand to the receptor active sites to insure the docking method was efficient and the active pocket was saved as MOE file to be used for docking simulation of the selected compounds.

Docking of the conformation database of the target compounds was done using MOE-Dock software. The following methodology was generally applied via loading of the enzyme active site file and the Dock tool was initiated. The MDB file of the ligand to be docked was loaded and Dock calculations were run automatically. The obtained poses were studied and the poses showed best ligand-enzyme interactions were selected and stored for energy calculations. The 2D interaction and stereo view for compounds **3, 6a** and **13** inside the active site of B-Raf enzyme were obtained and saved as both MOE and photo files. (cf. Figures. part (Fig. 2, 3 and 4)).

CONCLUSIONS

In this work we designed and synthesized some nitrogen containing heterocycles such as pyrrolone, benzoxazinone, thiazolidinone, oxadiazole and pyridazinone derivatives, to use them as anticancer agents against three types of carcinoma cell lines (HePG 2, HCT116 and PC3), using *Doxorubicin* as a reference drug. The binding modes and orientation of the most promising anticancer compounds **3**, **6a** and **13** at the active site of the ATP binding site of B-Raf kinase were studied. The result revealed that some of the new compounds showed high activities. Compound **6a** was more potent than the standard drug.

EXPERIMENTAL PART

Chemistry

Melting points were measured on a Gallen Kamp electric melting point apparatus and are uncorrected. The infrared spectra were recorded using potassium bromide disks on FTIR

Thermo Electron Nicolet 7600 (USA) infrared spectrometer at the Central laboratory of Faculty of Science, Ain shams University. The ^{1}H-NMR spectra were run at 300 MHz on a GEMINI 300 BB NMR spectrometer using tetramethyl silane (TMS) as internal standard in deuterated dimethylsulphoxide (DMSO-d_6) at the Main Defense Chemical laboratory. The mass spectra were recorded on a shimadzu GC-MS QP- 1000EX mass spectrometer operating at 70 ev at the Micro analytical Center of Cairo university. The reactions were monitored by the thin layer chromatography using Merck Kiesel gel 60 F_{254} aluminum backed plates. The biological activity was performed at Central Laboratory for Genetic Engineering, National Research Center, Dokki, Cairo, Egypt.

Action Of Ammonium Acetate On Furanone 1

A mixture of furanone **1** (10 mmol) and ammonium acetate (40 mmol) was heated in a sand bath at 150-160 ^{o}C for 2 hrs. The reaction mixture was cooled then poured onto water. The obtained solid was filtered off and dried, recrystallized from ethanol/dioxane mixture (1:1) to give the pyrrolone **2**.

*3-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-5-phenyl-1H-pyrrol-2(3H)-one **2***

Orange crystals; mp.294-296 ^{o}C. yield 83%. Anal. Calcd.for $C_{26}H_{19}N_3O$ (389.15): C, 80.18; H, 4.92; N, 10.79. Found: C, 80.22; H, 4.85; N, 10.71. FTIR (KBr) (νmax, cm^{-1}):3142 (NH),3059 (aryl-H), 1699 (C=O), 1617 (C=N),755, 686 (δ5H). ^{1}H-NMR (DMSO-d6): δH(ppm) 10.49 (s, 1H, NH, D_2O-exchangeable), 9.17 (s, 1H, C-

$H_{Pyrazole}$),8.09-7.39 (m, 15H, Ar-H),7.08 (s, 1H, C-$H_{Pyrrolone}$), 7.00 (s, 1H, =CH). MS (m/z, %): 389 ($M^{+\cdot}$,15), 345 (31), 289 (23), 256 (24), 181 (32), 105 (100), 77 (41), 64(54).

General Procedure For The Reaction Of Furanone 1 With Ethylenediamine And Ethanolamine

To a solution of furanone **1** (5 mmol) in absolute ethanol or dioxane (20 ml), ethylenediamine or ethanolamine (5 mmol) was added with stirring. The reaction mixture was stirred for 10 hrs. at room temperature. The solvent was evaporated under reduced pressure. The residue was triturated with light petroleum recrystallized from benzene to give the amide derivatives **6a** and **6b**, respectively.

N-(2-Aminoethyl)-2-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-4-oxo-4-phenylbutanamide ***6a***

Pale yellow crystals, mp. 115-117 ^{o}C (Light Petroleum), yield 68%.Anal. Calcd.for $C_{28}H_{26}N_4O_2$ (450.21): C, 74.65; H, 5.82; N, 12.44. Found: C, 74.69; H, 5.76; N, 12.40. FTIR, (KBr) (νmax, cm^{-1}): 3359, 3290 (NH, NH_2), 3058, 3028 (Aryl-H), 2953, 2924 (Alkyl-H), 1684,1653 (C=O), 762, 702 (δ5H). ^{1}H-NMR (DMSO-d6): δH(ppm) 8.70 (s, 1H, NH, D_2O-Exchangeable), 8.28 (s, 1H, C-HPyrazole),8.15-7.27 (m, 15H, Ar-H),7.21 (s, 1H, =CH), 3.82 (t, 2H, CH_2NH, J= 6.5 Hz), 3.77 (s, 2H, CH_2CO), 3.45 (t, 2H, CH_2NH_2, J= 6.3 Hz), 5.21 (br.s, 2H, NH_2, D_2O-Exchangeable). MS (m/z, %): 450 ($M^{+\cdot}$,11), 432 (31), 391 (15), 258 (100), 229 (12), 105 (27), 77 (100), 64(24).

2-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-N-(2-hydroxyethyl)-4-oxo-4-phenylbutanamide ***6b***

6b: Yellow crystals, mp. 129-131 ^{o}C (Light Petroleum), yield 72%.Anal. Calcd.for $C_{28}H_{25}N_3O_3$ (451.19):C, 74.48; H, 5.58; N, 9.31. Found: C, 74.42; H, 5.63; N, 9.25. FTIR,(KBr) (νmax, cm^{-1}): 3278 (br. OH), 3060, 3030 (Aryl-H), 2950, 2927 (Alkyl-H), 1677,1648 (C=O), 762, 701 (δ5H). ^{1}H-NMR (DMSO-d6): δH(ppm) 10.01 (s, 1H, NH, D_2O-Exchangeable), 8.32 (s, 1H, C-$H_{Pyrazole}$), 8.01-7.10 (m,16H, Ar-H),4.43 (t, 2H, CH_2O, J=5.4 Hz), 3.99 (t, 2H, CH_2N, J= 5.4 Hz), 3.72 (s, 2H, CH_2CO), 4.87 (br.s, 1H, OH, D_2O-Exchangeable).MS (m/z, %): 452 (M+1, 0.9),451 ($M^{+\cdot}$,10), 433 (M-.OH, 70), 402 (22), 286 (6), 231 (30), 167 (9), 104 (40), 77 (71), 64(100), 55 (17).

SUPPLEMENTAL MATERIAL

(Full experimental detail, tables, figures and results of biological testing) This material can be found as supplemental data on the publisher's website.

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Table 1 Cytotoxic effect on human cell lines (HePG 2, HCT116and PC3)

Sample Code	HePG 2		**HCT116**		**PC3**	
	LC_{50} (µg/ml)	**LC_{90}** (µg/ml)	**LC_{50}** (µg/ml)	**LC_{90}** (µg/ml)	**LC_{50}** (µg/ml)	**LC_{90}** (µg/ml)
3	**49.0**	**86.1**	**14.1**	**22.5**	**11.6**	**21.0**
5	--------	--------			--------	--------
6a		**100% up to 6.25ppm**		**100% up to 6.5 ppm**	**7**	**12.4**
7	--------	--------			**79.6**	**132.8**
8	--------	--------			--------	--------
10	--------	--------			--------	--------
12	**46.3**	**74.5**	**76.1**	**125.4**	**70.6**	**119.2**
13	**13.9**	**25.2**	**70.5**	**114.9**	--------	--------
14	--------	--------			--------	--------
15	--------	--------			--------	--------
16	--------	--------			--------	--------
18	--------	--------			--------	--------
DMSO	--------	--------	--------	--------	--------	--------
Negative control	--------	--------	--------	--------	--------	--------
Doxorubicin	**21.6**		**37.6**		**23.8**	

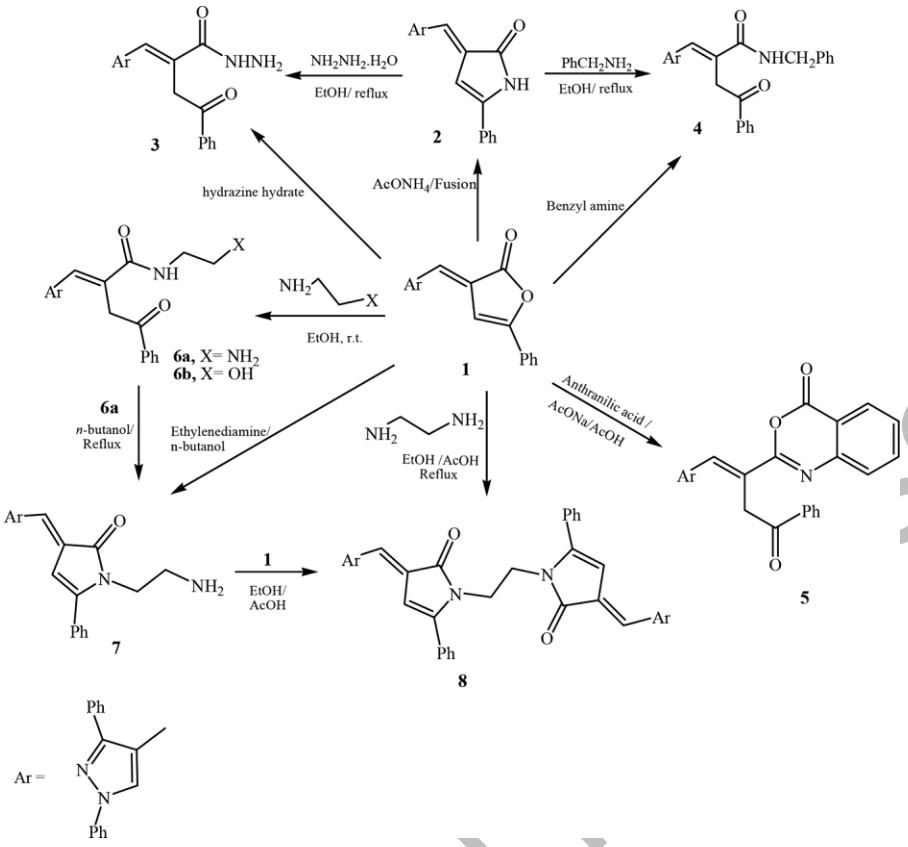
LC_{50}: Lethal concentration of the sample which causes the death of 50% of cells in 48 hrs

LC_{90}: Lethal concentration of the sample which causes the death of 90% of cells in 48 hrs)

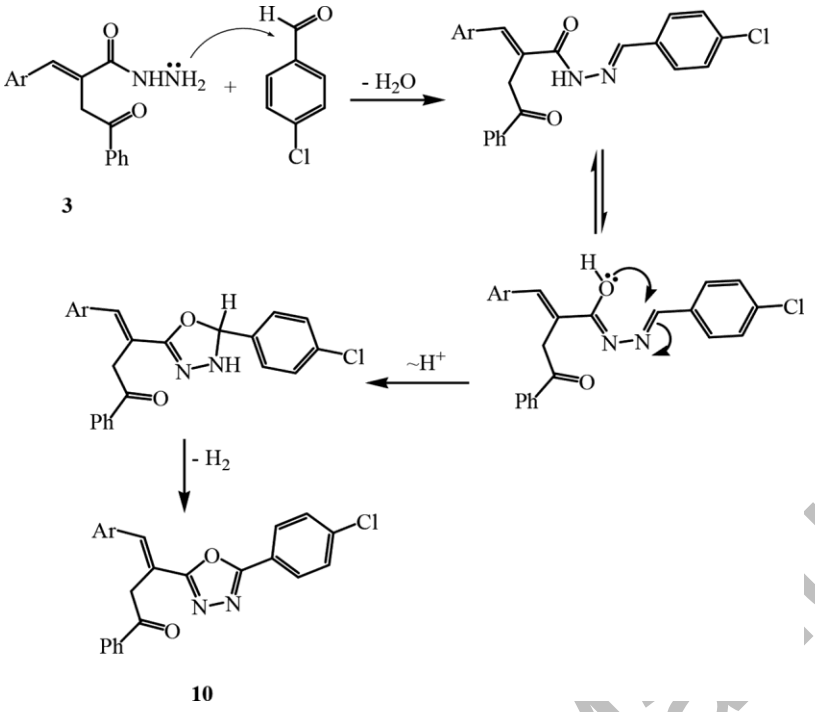
Table 2 Docking results of the compounds 3, 6a and 13 with B-Raf kinase in comparison with the ligand SM5 using MOE software version 2008.10.

Compd. NO.	Docking score (Kcal/mol)	Amino acid residues (bond length A^o)	Atoms of compound	Type of bond
SM5	-6.38	Cys532(2.7);	N(pyridine);	H-don
		Glu501(2.1);	OH;	H-don
		Lys483(2.4);	OH;	H-don
		Trp531;	Pyridine;	Arene-Arene
		Phe583	Pyridine, pyrazole	Arene-Arene
3	-7.24	Ser465(2.7), (2.9);	$N(NH_2)$;	H-acc, H-don
		Ser535(2.7);	O(COPh);	H-acc
		Ser536(3);	O(COPh);	H-acc
		Trp531;	3-Phenyl;	Arene-Arene
		Phe583	3-Phenyl	Arene-Arene
6a	-6.32	Ser535(2.7);	O(COPh);	H-acc
		Ser536(2.9);	O(COPh);	H-acc
		Asn581(3.2),	$H(NH_2)$;	H-don
		Asp594(1.7);	$H(NH_2)$;	H-don
		Phe583	3-Phenyl	Arene-Arene
13	-8.43	Ser535(3);	O(COPh);	H-acc
		Ser535(2.8);	$O(COCH_3)$;	H-acc
		Ser536(3);	O(COPh);	H-acc
		Phe583	3-Phenyl	Arene-Arene

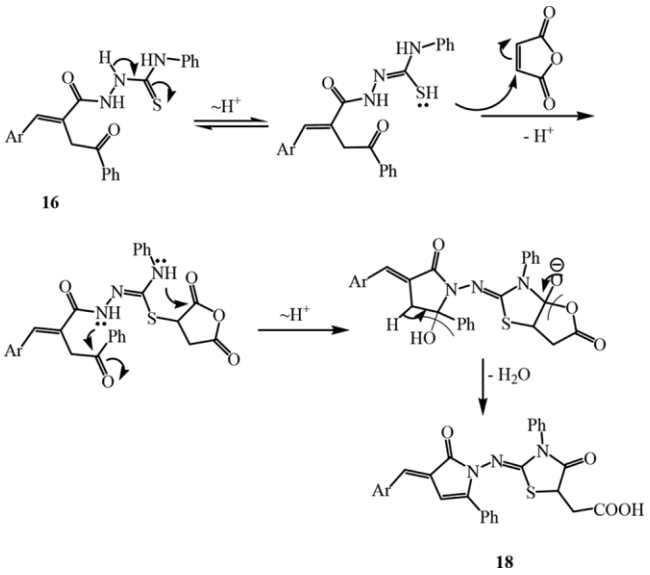
Scheme 1.



Scheme 2. (Formation of oxadiazole **10**)



Scheme 3. (Formation of thiazolidinone derivative **18**)



Scheme 4.

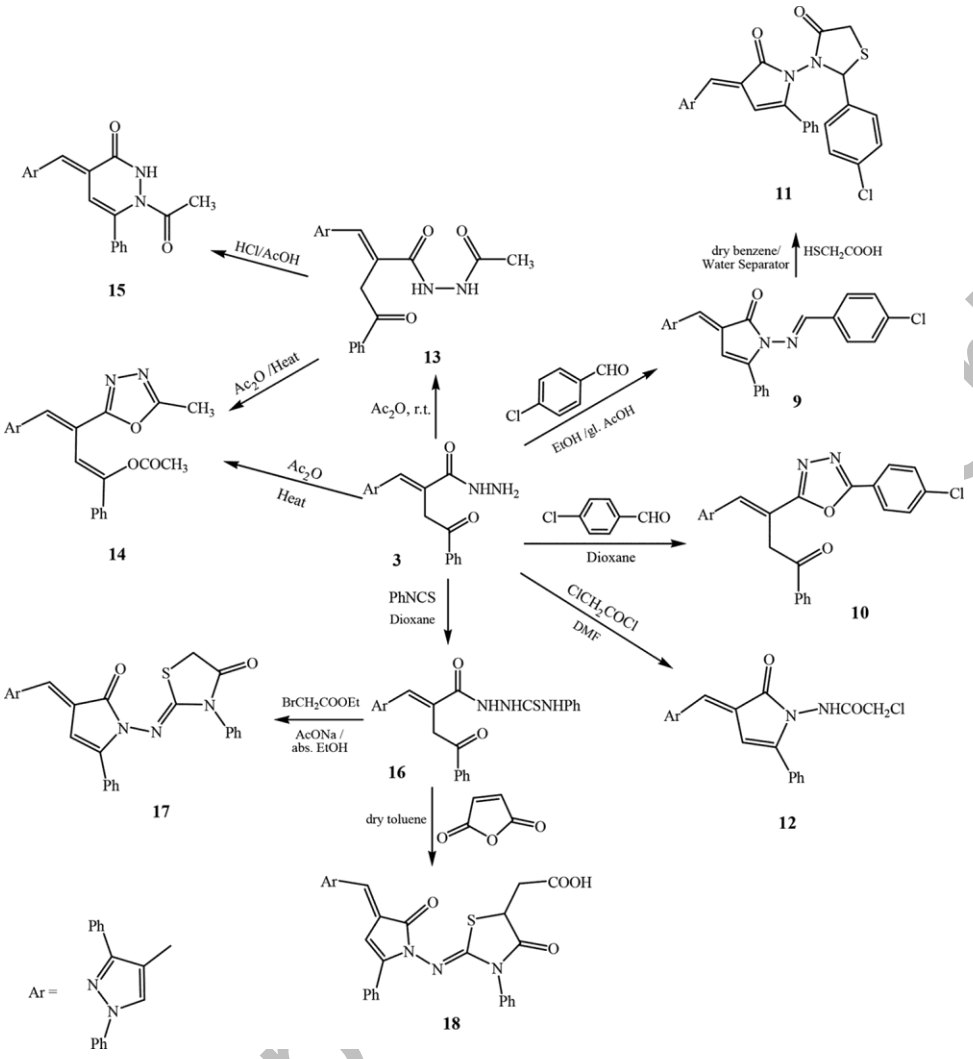
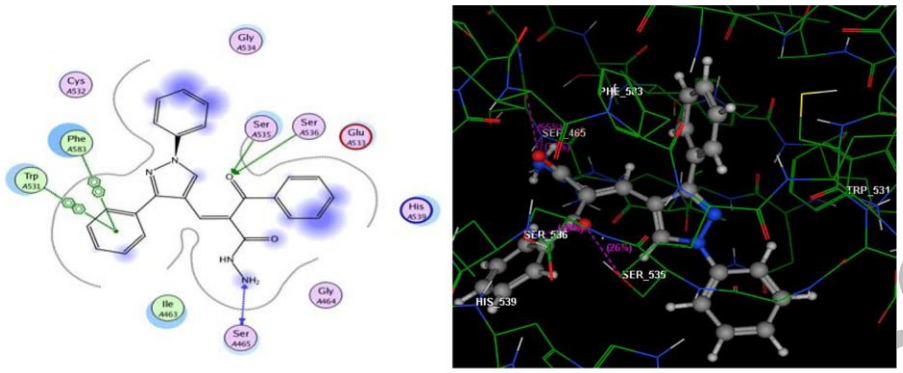
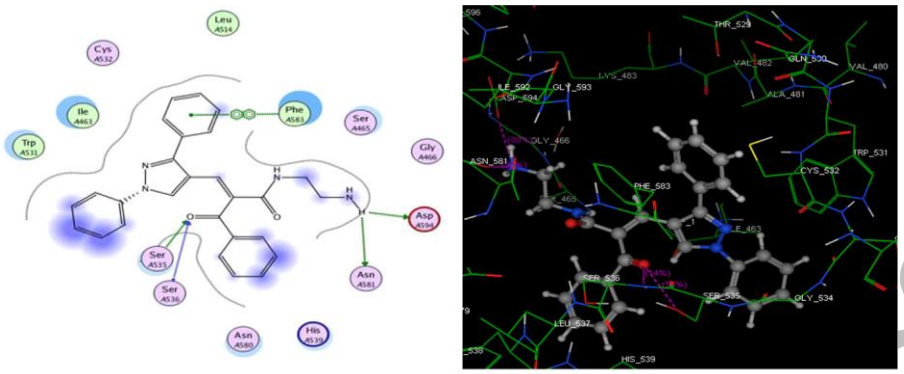


Fig. 1. The proposed binding mode of compound **3** docked in the active site of B-Raf; A and B showing 2D and 3D ligand-receptor interactions (hydrogen bonds are illustrated as arrows; C atoms are colored gray, N blue and O red).



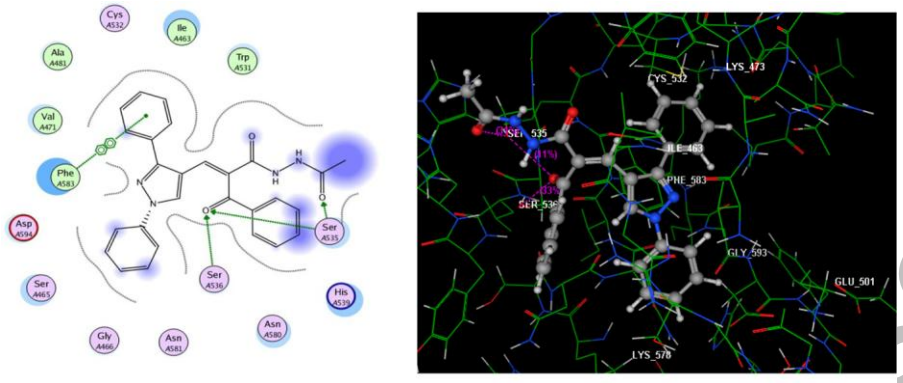
(a) (b)

Fig. 2. The proposed binding mode of compound **6a** docked in the active site of B-Raf; A and B showing 2D and 3D ligand-receptor interactions (hydrogen bonds are illustrated as arrows; C atoms are colored gray, N blue and O red).



(a) (b)

Fig. 3. The proposed binding mode of compound **13** docked in the active site of B-Raf; A and B showing 2D and 3D ligand-receptor interactions (hydrogen bonds are illustrated as arrows; C atoms are colored gray, N blue and O red).



(a) (b)