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Spectroscopic Investigation And Computational Study Of Some Thieno[2,3-D]Pyrimidine Compounds

Suliman Mohamed Mussa*, Salem El-tohami Ashoor, Lamia Ahmed Albahi
[1]Chemistry Department, Faculty Of Science, Misurata University, Misurata, Libya
*Corresponding Author: suliman@gmail.com

Abstract

The present work is aimed to synthesize and computational study of some heterocyclic compounds containing thieno[2,3-d]pyrimidines. Moreover some of the synthesized compounds were tested in vitro against breast carcinoma. Compound 1 was reacted with chloroacetonitrile in the presence of anhydrous sodium acetate to give the cyanometylthio derivative which underwent cyclization upon treatment with ethanolic sodium ethoxide to give 5-amino-6-cyano-4-methyl-2-phenylthieno[2,3-d]pyrimidine 3 and N-acetylation of compound 3 by refluxing in acetic anhydride afforded N-(6-cyano-4-methyl-2-phenylthieno[2,3-d]pyrimidin-5-yl)acetamide 4. Also the o-aminocyano 3 was used as precursor intermediate to produce pyrimidithienopyrimidinone and pyrimidiothienopyrimidine derivatives 5 and 6 by reacting with formic acid and formamide respectevely. Refluxing of compound 7 with an excess amount of ammonia solution 35% gave N-(6-cyano-4-methyl-2-phenylthieno[2,3-d]pyrimidin-5-yl)formamidine (8) . Hydrazionlysis of compound 7 with hydrazine hydrate 99% in absolute ethanol gave the 7-Amino-8-imino-4-methyl-2-phenylpyrimido[4\,5\:4,5]thieno[2,3-d]pyrimidine (9), The latter compound underwent ring closure upon treatment with acetic anhydride to afford 4,8-Dimethyl-2-phenyltriazolo[1\\,5:1\,6\]pyrimido[4\,5\:4,5]thieno[2,3-d]pyrimidine (10). The total optimization interaction energy of these compounds had leads to an energy profile by DFT method.

Keywords: Synthesis , Mechanism, Thienopyrimidine, yrimidothienopyrimidine , Biological activity, Theoretical investigations, DFT.

1. Introduction

The formation of novel fused heterocycles is an important task for heterocyclic chemists from various points of view for the development of living things. Furthermore, many condensed heterocyclic systems, especially when linked to a pyrimidine ring as thienopyrimidine play an important role as potent analgesic [1], anti-inflammatory [1-5], antipyretic [6], antimicrobial [7], anticonvulsant [8], antiplatelet activities [9], and other central nervous system (CNS) affecting activities [10]. In addition, pyrimidine nucleus can be found in a broad variety of antibacterial[11], anticancer and anti-tumor agents [12] and as a continuation of our previous work about the synthesis of fused pyrimidine compounds [13-14] , we became interested in the synthesis of some heterocyclic compounds containing thieno [2,3-d] pyrimidne compounds.

2. Material and Methods

All melting points are uncorrected and measured on a Gallan-Kamp apparatus. IR spectra were recorded on a spectrophotometer FTIR TENSOR- 37 Bruker company or on FT-IR Microscope varian 660-IR central laboratory of medical researches Tripoli, Libya . 1HNMR spectra were measured on a Bruker 300 MHz Ultrashield TM . Elemental analyses were determined on a Perkin-Elmer 240C elemental analyzer or on an Elemental Analyses system GmbH VARIOEL V2,3 CHNS Mode Assiut University, Egypt. All physical properties and spectral data of the

synthesized compounds are listed in tables 1 and 2. FT-IR Theoretical investigations are performed by Density Functional Theory (DFT) method of B3LYP/6-31G+(2d,p) basis sets for all compounds 1 to 10.

5-Cyano-4-methyl-2-phenylpyrimidin-6(1H)-thione
(1):
This compound was prepared according to literature procedure[15-17]
5-Cyano-4-methyl-2-phenyl-6-cyanomethylthiopyrimidine (2):

A mixture of compound 1 (3.41g, 0.015 mol) , chloroactonitrile (1.13g, 0.015 mol) and sodium acetate (2.5g, 0.03 mol) in ethanol (50ml) was refluxed for 3hrs. and then allowed to cool . The solid product was collected and recrystallized from ethanol as yellow crystals.
5-Amino-6-cyano-4-methyl-2-phenylthieno[2,3-d]pyrimidine
(3):
A suspension of compound 2 (2.77g , 0.01mol) in absolute ethanol (50ml) containing sodium metal (0.23g) was heated under reflux for 1hr. The solid product was collected and recrystallized from dioxane as yellow crystals [16].
N-(6-cyano-4-methyl-2-phenylthieno[2,3-d]pyrimidin-5-yl)acetamide
(4):
A mixture of compound 3 (2.66g, 0.01 mol) and acetic anhydride (20 ml) was refluxed for 4hrs, then allowed to cool . The reaction mixture was poured into an ice\water mixture (100 ml) . The solid product was collected and recrystallized from dioxane as yellow crystals.
4-Methyl-2-phenylpyrimido[4\,5\:4,5]thieno[2,3-d]pyrimidin-8-one
(5):
A mixture of compound 3 (2.66g, 0.01 mol) and formic acid (30 ml) was refluxed for 4hrs, then allowed to cool . The reaction mixture was poured into an ice\water mixture (100 ml) . The solid product was collected and recrystallized from dioxane as pale yellow crystals.

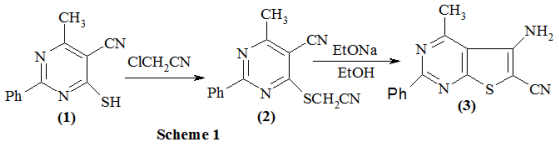
8-Amino-4-methyl-2-phenylpyrimido[4\,5\:4,5]thieno[2,3-d]pyrimidine
(6):
A mixture of compound 3 (2.66g, 0.01 mol) and formamide (20 ml) was refluxed for 3hrs, then allowed to cool . The reaction mixture was poured into an ice\water mixture (100 ml) . The solid product was collected and recrystallized from dioxane as yellow crystals.
6-cyano-5-ethoxymethyleneamino-4-methyl-2-phenylthieno[2,3-d]pyrimidine
(7):
A mixture of compound 3 (2.66g, 0.01 mol) , triethylorthoformate (1.66 ml, 0.01 mol) in acetic anhydride (20 ml) was refluxed for 5 hrs. , then allowed to cool .The solid product was collected and recrystallized from ethanol as yellow crystals.
N-(6-cyano-4-methyl-2-phenylthieno[2,3-d]pyrimidin-5-yl)formamidine
(8):
A mixture of compound 7 (1.61g, 0.005 mol) , ammonia solution35% (10 ml) in absolute ethanol (20 ml) was refluxed for 7 hrs. , then allowed to cool . The reaction mixture was poured into an ice\water mixture (100 ml) . The solid product was collected and recrystallized from dioxane as yellow crystals.
7-Amino-8-imino-4-methyl-2-phenylpyrimido[4\,5\:4,5]thieno[2,3-d]pyrimidine
(9):
A mixture of compound 7 (1.61g, 0.005 mol) , hydrazine hydrate 98% (10 ml) in absolute ethanol (10 ml) was heated at 50oC for 2 hrs. , then allowed to cool . The reaction mixture was poured into an ice\water mixture (100 ml) . The solid product was collected and recrystallized from dioxane as yellow crystals.
4,8-Dimethyl-2-phenyltriazolo[1\\,5\\:1\,6\]pyrimido[4\,5\:4,5]thieno[2,3-d]pyrimidine
(10):
A mixture of compound 9 (1.54g, 0.005 mol) and acetic anhydride (20 ml) was refluxed for 4hrs, then allowed to cool . The reaction mixture was poured into an ice\water mixture (100 ml) . The solid product was collected and recrystallized from dioxane as yellow crystals.

Cell culture

Stock solution compounds was prepared by dissolving in 1.0 ml DMSO . The cell line purported to be human cell line was fed by media three times a week and the split once confluence was reached .(to split the cell , the medium was removed , the cells washed hanks buffered salt solution (HBSS) , then gently harvested with 1.0 ml detachment trypsin neutralizing solution). Once all the cells loosed from the plate, and be in solution 1.0 ml of detached trypsin neutralizing solution was added. This solution was pipette into a sterile falcon tube which centrifuged at 1300 rpm for 5 mints, the supernatant was removed and the pellet resuspended in an appropriate volume of media . This mixture was then placed into fresh culture flasks at 1:2 split ratio. Cells plated into a plate in 1.0 ml cell suspension , The concentration of (5x106 cells/ml) in RPMI1640 (media) supplemental with heat–inactivated 10% FBS, 0.2 mg /l, L-glutamide, 1.0 mg/ml $NaHCO_3$, 100 units/ml penicillin and 100 units/ml streptomycin and then incubated in a humidified incubator at 37 oC and 5% CO_2 atmosphere. The cells were allowed to attach for 24 hr. At end of one week of incubation, the cells were harvested . The duplicate plats were then used for screening the compounds. Media in each flask was changed three times in one week (every other day) and treated by compound after changing. This is used in concentration 0.001 mM/ml, 50 µl DMSO was used as control (-v control). Cheek proliferation rate daily microscopically and compare with –v control proliferation rate .

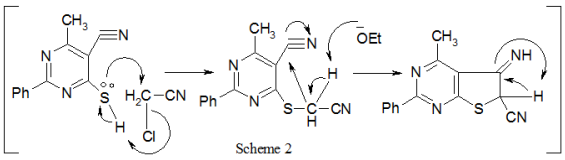
3. Results and Discussion

Compound 1 was reacted with chloroacetonitrile in the presence of anhydrous sodium acetate to give the cyanometylthio derivative which underwent intramolecular Thrope-Ziegler cyclization upon treatment with ethanolic sodium ethoxide to give 5-amino-6-cyano-4-methyl-2-phenylthieno[2,3-d]
pyrimidine 3 scheme 1.



Scheme 1

The possible mechanism for formation of compound 3 can be explained by the reaction pathway depicted in scheme 2 .



Scheme 2

The IR spectrum of compound 2 and 3 revealed the appearance of characteristic absorption bands at 3230, 3226 cm-1 for (NH_2) group in compound 3 Figure (3.1,2).

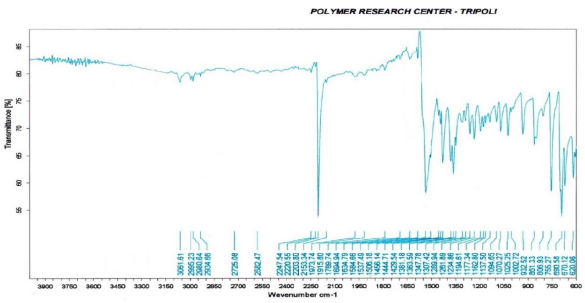


Figure 3.1

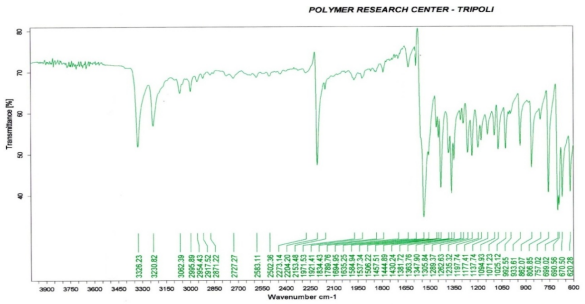


Figure 3.2

Furthermore 1HNMR spectrum of compound 3 confirmed the cyclization by disappearance of the signal at d = 4.1 for -SCH2- protons and showed a singlet at d = 7.0 for (-NH2) group which disappeared in the spectrum with addition of D2O Figure (3.3,4).

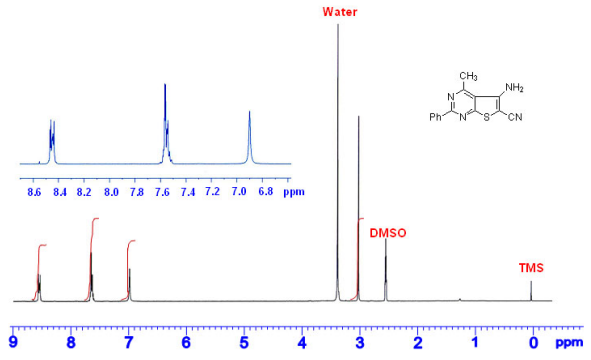


Figure 3.3

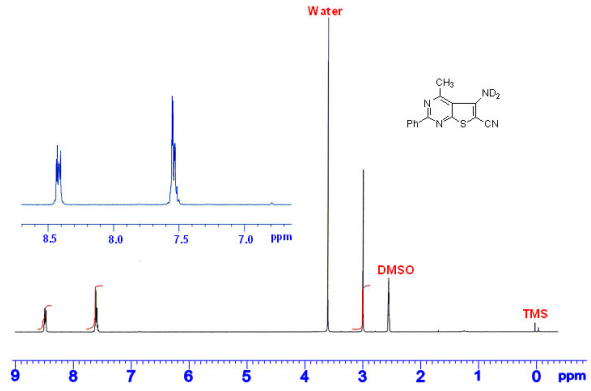
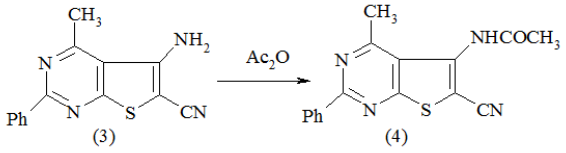
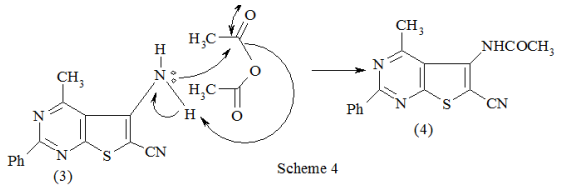


Figure 3.4

N-acetylation of compound 3 by refluxing in acetic anhydride afforded N-(6-cyano-4-methyl-2-phenyl thieno[2,3-d]pyrimidin-5-yl)acetamide 4 . Scheme 3 .



Scheme 3



Scheme 4

The IR spectrum of compound 4 revealed the appearance of characteristic absorption band at 1646 cm-1 for acetyl group Figure (3.5) .

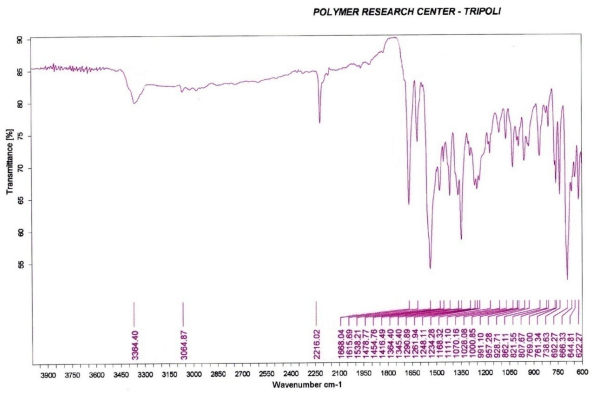
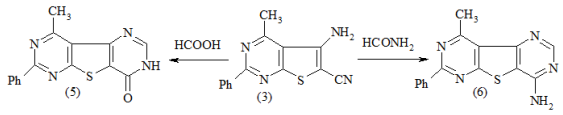


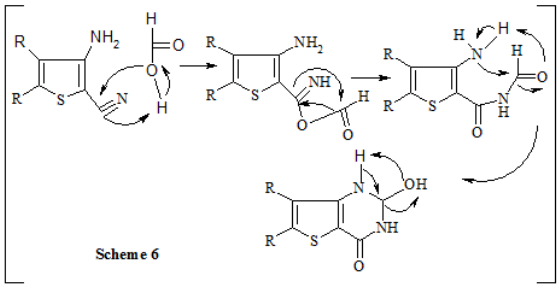
Figure 3.5

Also the o-aminocyano 3 was used as precursor intermediate to produce pyrimidithienopyrimidinone and pyrimidiothienopyrimidine derivatives 5 and 6 by reacting with formic acid and formamide respectevely (Scheme 5).



Scheme 5

The possible mechanism for formation of compound 5 can be explained by the reaction pathway depicted in scheme 6.



Scheme 6

The IR spectrum of compound 5 revealed the disappearance of characteristic absorption band at 2216 cm-1 for (CN) group and appearance of characteristic absorption bands at 1646 cm-1 for (CO) pyrimidinone Figure (3.6).

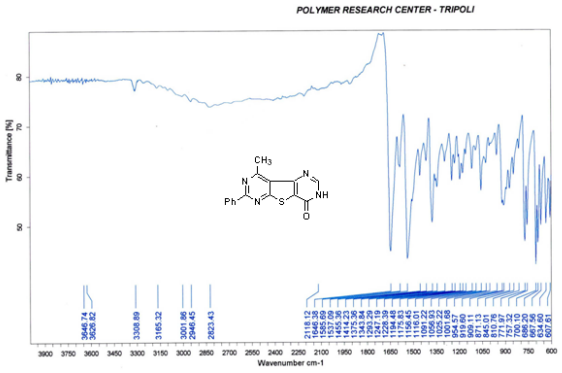


Figure 3.6

Furthermore 1HNMR spectrum of compound 5 showed a singlet signal at d = 8.2 for (-N=CH-N-) Figure (3.7) .

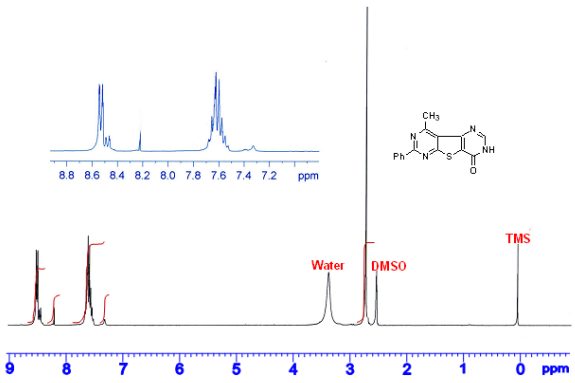
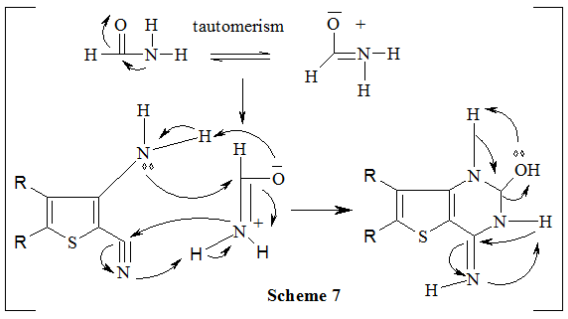


Figure 3.7

The possible mechanism for formation of compound 6 can be explained by the reaction pathway depicted in scheme 7.



Scheme 7

The IR spectrum of compound 6 revealed the disappearance of characteristic absorption band at 2216 cm-1 for (CN) group and appearance of characteristic absorption bands at 1646 cm-1 for (CO) pyrimidinone . Figure (3.8).

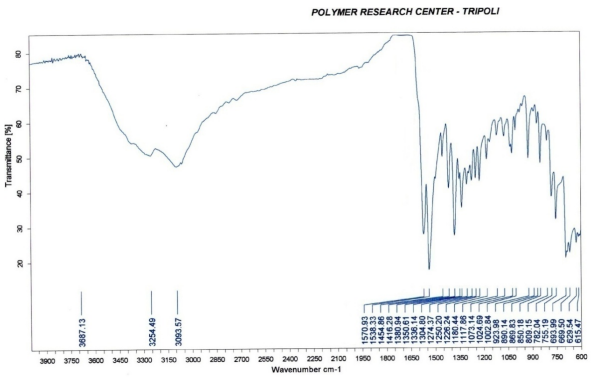


Figure 3.8

Furthermore 1HNMR spectrum of compound 6 showed a singlet signal at d = 8.7 for (-N=CH-N-) Figure (3.9).

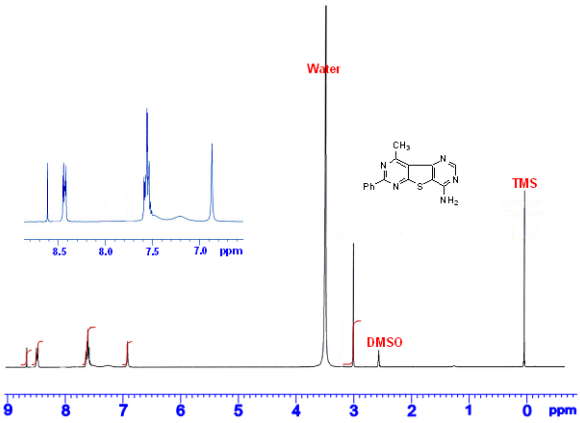
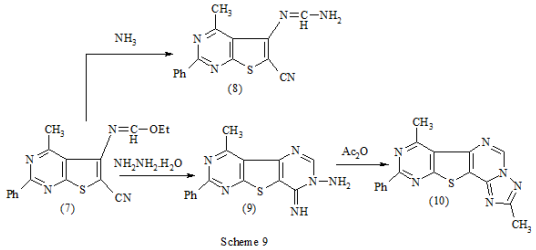


Figure 3.9

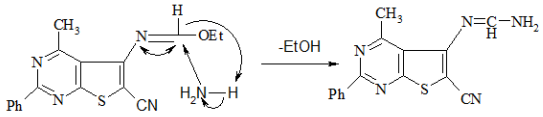
Refluxing of compound 7 with an excess amount of ammonia solution 35% gave N-(6-cyano-4-methyl-2-phenylthieno[2,3-d]pyrimidin-5-yl)formamidine (8) Scheme 9.



Scheme 9

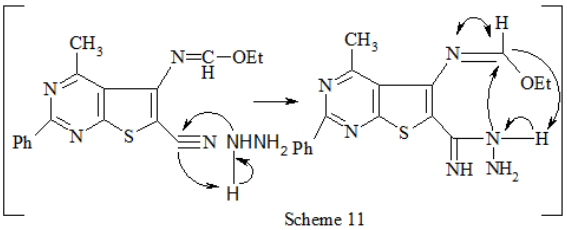
The possible mechanism for formation of compound

8 can be explained by the reaction pathway depicted in scheme 10.

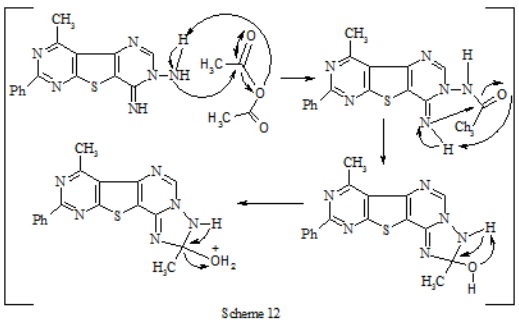


Scheme 10

The IR spectrum of compound 8 revealed the appearance of characteristic absorption bands at 3303, 3232 cm-1for (NH2) group . Furthermore 1HNMR spectrum of compound 8 showed the disappearance of signals at d = 1.3-1.4 (t , 3H, Et) and 4.4-4.5 (q, 2H, Et). Hydrazionlysis of compound 7 with hydrazine hydrate 99% in absolute ethanol gave the 7-Amino-8-imino-4-methyl-2-phenylpyrimido [4\,5\ :4,5] thieno [2,3-d] pyrimidine (9) , The latter compound underwent ring closure upon treatment with acetic anhydride to afford 4,8-Dimethyl-2-phenyltriazolo [1\\,5\\:1\,6\] pyrimido [4\,5\:4,5] thieno [2,3-d]- pyrimidine (10) . The possible mechanism for formation of compounds 9 and 10 can be explained by the reaction pathway depicted in scheme 11 and 12 respectively.



Scheme 11



Scheme 12

The free energy profiles have been established of the reaction of some thieno[2,3-d]pyrimidine Compounds, then was reacted with chloroacetonitrile to get compound 2, was followed by ethanolic sodium ethoxide, acetic anhydride or o-aminocyano, formic acid, formamide, ammonia and hydrazine hydrate to offered compounds 3, 4, 5, 6, 7, 8 and 9 respectively. Compound 9 underwent ring closure upon treatment with acetic anhydride to afford compound 10 as final product. The total optimal interaction energy of these compounds leads to an energy profile characterized by a deep minimum at (-775549.47kcal/mol) of compound 8, after this point, a second minimum less deep than the previous one is observed at at (-713559.034 kcal/mol) of compound 10, followed by compounds 6 and 7 at (-692710.3716 kcal/mol). compounds 4 and 5 are at (-668348.3211 kcal/mol and -644018.4876 kcal/mol) respectivly. Compounds 3 and 2 are seam were found at (-573446.4177 kcal/mol and -574554.8383 kcal/mol). (-492332.061 kcal/mol) was found for compound 1. Figure (3.10). Blue color shows the free energy goes from high to low and red color shows the free energy increase from low to high.

Biological activity

The compounds (3, 4, 6 & 7) were screened in vitro for their biological activity against breast carcinoma in concentration of 200 µM using DMSO as solvent . The results revealed that the compounds: 3,4 and 7 exhibit high activity against breast carcinoma. Table 3

4. Conclusion

A part of our continuous search , a serious of thienopyrimidine derivatives were synthesized. The products were obtained in good yields, which have been unambiguously characterized by spectra and Theioretical investigation of free energy profile for compounds 1-10. We found the compound 8 has the deep minimum at (-775549.47kcal/mol). Some synthesized compounds were screened in vitro for their biological activity against breast carcinoma. Three compounds 3, 4 and 7 were found to possess high activity. We hope that in the future many new biological profiles will be added to it .

Acknowledgment

The authors Thanks Eain Shmesh- Egypt for using FT-IR and HNMR and also Misurata Universit for using the labs resources University.

Table 3.1: physical properties and analytical data for compounds(2-10)

No	m.p ^{o}C	Yield %	Formula/mol.wt	Calculated / Found			
				C	H	N	S
2	257-260	85	$C_{14}H_{10}N_4S$ 266.32	62.99 63.14	3.86 3.78	20.97 21.04	11.95 12.04
3	>320	87	$C_{14}H_{10}N_4S$ 266.32	62.99 63.04	3.86 3.78	20.97 21.04	11.95 12.00
4	176-177	50	$C_{16}H_{12}N_4OS$ 308.36	62.24 62.30	4.02 3.92	18.07 18.16	10.33 10.40
5	255-256	71	$C_{15}H_{10}N_4OS$ 294.33	61.13 61.07	3.48 3.42	18.93 19.04	10.77 10.89
6	268-269	47	$C_{15}H_{11}N_5S$ 293.07	61.31 61.42	3.82 3.78	23.75 23.87	10.81 10.93
7	140-141	68	$C_{17}H_{14}N_4OS$ 322.38	63.07 63.33	4.51 4.38	17.61 17.38	8.88 9.95
8	220-221	60	$C_{15}H_{11}N_5S$ 293.35	61.30 61.42	3.81 3.78	23.83 23.87	10.85 10.93
9	274-276	74	$C_{15}H_{12}N_6S$ 308.36	58.30 58.43	4.01 3.92	27.13 27.25	10.32 10.40
10	>320	65	$C_{17}H_{12}N_6S$ 332.38	61.43 61.60	3.64 3.60	25.28 25.18	9.65 9.48

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Table 3.2: Spectroscopic Data of Compounds (2-10)

2	IR: υ = 2203 cm-1 (C N). 1HNMR(DMSO-d6) : d = 2.68 (s,3H, CH3 , pyrimidine), 4.1 (s, 2H, S-CH2), 7.5-7.7 (m, 3H, Ar-H) and 8.5-8.6 (m, 2H, Ar-H .
3	IR: υ = 3230, 3226 cm-1 (NH2) and 2203cm-1 (C N) . 1HNMR(DMSO-d6) : d = 3.0 (s,3H, CH3 , pyrimidine), 7.0 (s, 2H, NH2), 7.5-7.7 (m, 3H, Ar-H) and 8.5-8.6 (m, 2H, Ar-H .
4	IR: υ = IR: υ = 3362 (NH) and 2216 cm-1 (C N) . 1HNMR(DMSO-d6): d = 2.6 (s, 3H, CH3, COCH3), 2.8 (s,3H, CH3, pyrimidine), 6.9 (s, 1H, NH), 7.5-7.7 (m, 3H, Ar-H), and 8.4-8.6 (m, 2H, Ar-H) .
5	IR: υ = IR: υ = 3308 (NH) and 1646 cm-1 (C=O). 1HNMR(DMSO-d6): d = 2.8 (s,3H, CH3, pyrimidine), 7.3 (s, 1H, NH), 7.5-7.7 (m, 3H, Ar-H), 8.2 (s,1H,CHpyrimidine) and 8.4-8.6 (m, 2H, Ar-H) .
6	IR: υ = IR: υ = 3254, 3093 (NH2). 1HNMR(DMSO-d6): d = 3.0 (s,3H, CH3, pyrimidine), 6.9 (s, 2H, NH2), 7.5-7.6 (m, 3H, Ar-H), 8.4-8.5(m, 2H, Ar-H) and 8.7 (s,1H,CHpyrimidine)
7	IR: υ = 2209 cm-1 (C N). 1HNMR(DMSO-d6): d = 1.3-1.4 (t , 3H, Et), 2.9 (s, 3H, CH3, pyrimidine), 4.4-4.5 (q, 2H, Et), 7.5-7.6 (m, 3H, Ar-H), 8.4 (s, 1H, N=CH) and 8.5-8.6(m, 2H, Ar-H) .
8	IR: υ = 3303, 3232 cm-1(NH2) and 2205 cm-1 (C N). 1HNMR(DMSO-d6): d = 3.0 (s, 3H, CH3, pyrimidine), 3.2 (s, 2H, NH2), 7.5-7.6 (m, 3H, Ar-H), 8.4-8.5(m, 2H, Ar-H) and 8.7 (s, 1H, N=CH) .
9	IR: υ = 3334 cm-1(NH) and 3177, 3052 cm-1 (NH2). 1HNMR(DMSO-d6) : d = 3.0 (s, 3H, CH3, pyrimidine), 5.9(s, 2H, NH2), 7.4 (s, 1H, NH) 7.5-7.6 (m, 3H, Ar-H), 8.3 (s,1H,CHpyrimidine) and 8.5-8.6(m, 2H, Ar-H) .
10	IR: υ = 1600 cm-1 (-C=N-) . 1HNMR(DMSO-d6): d = 3.0 (s,3H, CH3, pyrimidine), 3.8 (s. 3H, CH3, triazole), 7.5-7.6 (m, 3H, Ar-H), 8.5-8.6(m, 2H, Ar-H) and 8.9 (s,1H,CHpyrimidine) .

Table 3.3: Activity against breast carcinoma

Compound	The effect after 24 hr	The effect after 96 hr	The effect after 144 hr	The effect after 196-2 hr
Control	Normal	Normal	Normal	Normal
DMSO	No effect	No effect	No effect	No effect
3	75%	80%		
4	No effect	No effect	70%	70%
6	No effect	No effect	30%	30%
7	50%	70%		
8	No effect	No effect	No effect	40%
9	No effect	No effect	50%	70%

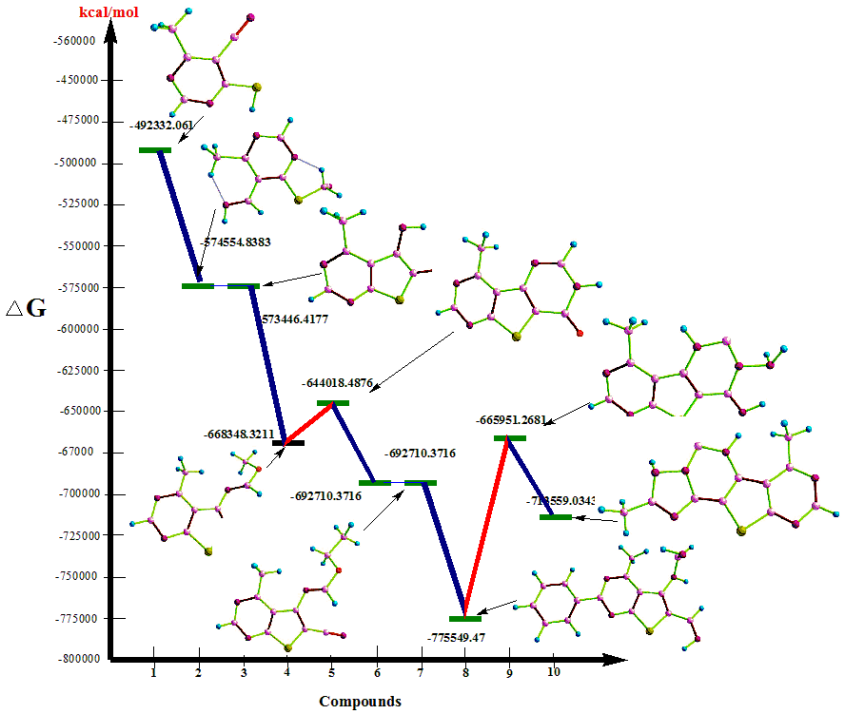

Figure 3.10: Free energy profile for compounds 1-10, ball and stick structures of the computed species with geometrical parameter

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