ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Synthesis and antifungal evaluation of some new heterocycles incorporating naphthalene moiety

Sobhi M. Gomha[1] and *Mohamed G. Badrey[2]

1. Department of Chemistry, Faculty of Science, University of Cairo, Giza, 12613, Egypt.

2. Chemistry Department; Faculty of Science; Fayoum University, El-Fayoum, Egypt.

Manuscript Info

Manuscript History:

Received: 14 October 2013
Final Accepted: 24 October 2013
Published Online: November 2013

Key words:
2-Cyanoacetohydrazide, aminopyrazole, 1, 2-dihydropyridine, 2,3-dihydrothiazole and antifungal activity.

Abstract

The reaction of 2-cyano-N'-(1-(naphthalen-2-yl)ethylidene)acetohydrazide **1** with the aromatic aldehydes afforded the corresponding arylidene derivatives **3a-e**. Refluxing of the latter product **3a** with hydrazine hydrate gave the aminopyrazole derivative **4**. Compound **1** was utilized as key intermediate for the synthesis of some new 1,2-dihydropyridine **7** and 2,3-dihydrothiazole **8** derivatives. Treatment of **8** with triethylorthoformate in acetic anhydride yielded 2,3-dihydrothiazolo[4,5-d]pyrimidinone **9.** Moreover, reaction of **1** with phenyl isothiocyanate gave the corresponding thioacetanilide **10**. The latter compound **10** was used for the synthesis of thiadiazole **12**. The structures of all new compounds were elucidated on the basis of elemental analysis and spectral data. Twelve of the synthesized products were evaluated as antifungal agents.

Introduction

Plenty of interesting and useful annulated heterocyclic systems have been synthesized using hydrazine and its derivatives; one of these derivatives is cyanoacetic acid hydrazide that can condense with various carbonyl compounds to afford the corresponding hydrazones. The urgent and insisting need for synthesis of new heterocyclic compounds related to the named hydrazide such as thiophenes, azines and coumarins is due to their pharmalogical actions; these compounds could be used as antimicrobial [1,2], antitubercular [3,4], anticonvulsant [5,6] anti-inflammatory [7,8], antidepressant [9], antitumor [10], and analgesic activities [11]. In addition, pyridinecarbonitriles have been known to posses antihypertensive [12], antihistaminic [13], anticancer [14], in addition to antibacterial [15-17] or antifungal actions [16-18]. In this article we use cyanoacetic acid hydrazide as a prestarting material for synthesis of some interesting heterocycles.

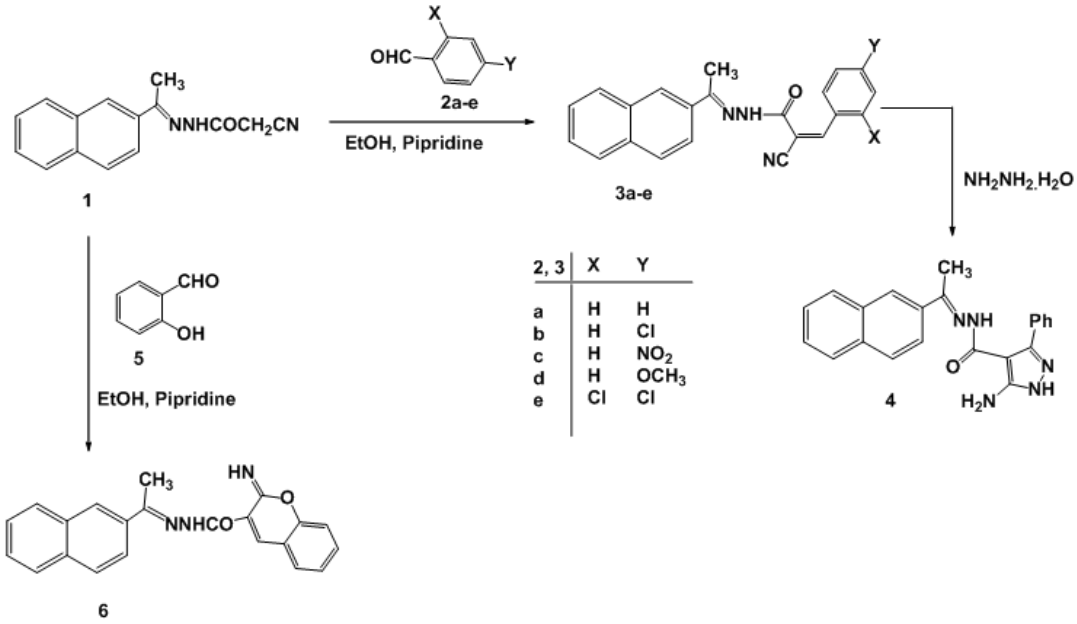
2. Result and Discussion

1.1. Chemistry

The target compound **1** was prepared through condensation between 2-acetylnaphthalene and cyanoacetic hydrazide in refluxing ethanol containing catalytic amount of piperidine [19].

The hydrazone derivative **1** and its versatile role as synthetic intermediate is ideally suited as it contains more than functional group which could be used as building unit for new and promising compounds in one or two easy reaction steps. It was subjected to various chemical reactions to give new products; first of which the condensation with aromatic aldehydes **2a-e** in ethanol/piperidine. All aldehydes gave the corresponding arylidenes **3a-e** in moderate to good yields except for salicylaldehyde which afforded the coumarin derivative **6** and the formation of coumarins through such reaction is well known in literature [20, 21]. Structures of compounds **3a-e** were confirmed via their spectral data; IR would show no marked change but still showed the stretching vibrations of NH, CN and CO groups at the ranges 3423-344, 2203-2217, 1614-1665 cm^{-1} respectively. In addition, mass spectra of all derivatives displayed all correct molecular ion peaks. The IR spectrum of compound **6** lacked an absorption band of CN group which suggest its participation in cyclization process, the mass spectrum would show no difference between the cyclized and uncyclized products but still give the correct molecular ion peak at m/z = 355; further confirmation of

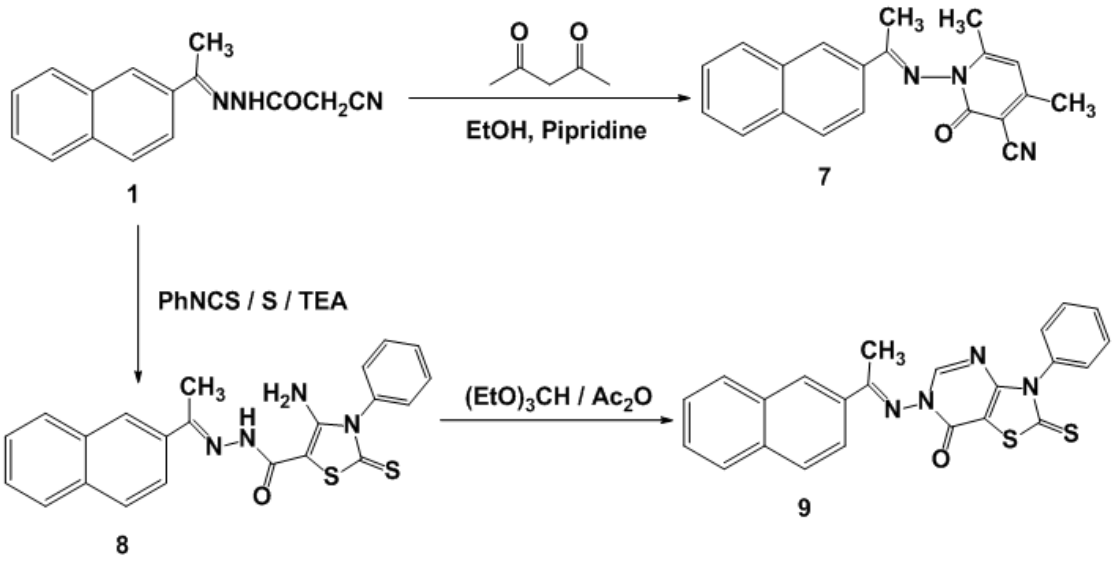
the coumarin structure **6** was gained from ^{1}HNMR spectrum that displayed a characteristic signal at 8.63 ppm related to the 4-H pyran ring. A trial for cyclization of one derivative of compound **3** (X, Y = H) was performed through reaction with hydrazine hydrate which furnished the aminopyrazole derivative **4** in a good yield (Scheme1). The reaction probably started through Michael-like type addition of one NH_2 function of hydrazine to the arylidenes double bond of **3a** followed by a second addition of the second NH_2 group on cyano group to afford the pyrazole **4**. Structure elucidation of compound **5** based on IR spectrum which showed strong absorption peaks at 3443, 3245 cm^{-1} due to amino group, also disappearance of absorption band for CN group was observed; moreover, in mass spectrum a peak at m/z = 369 is consistent with the proposed structure.



Scheme1

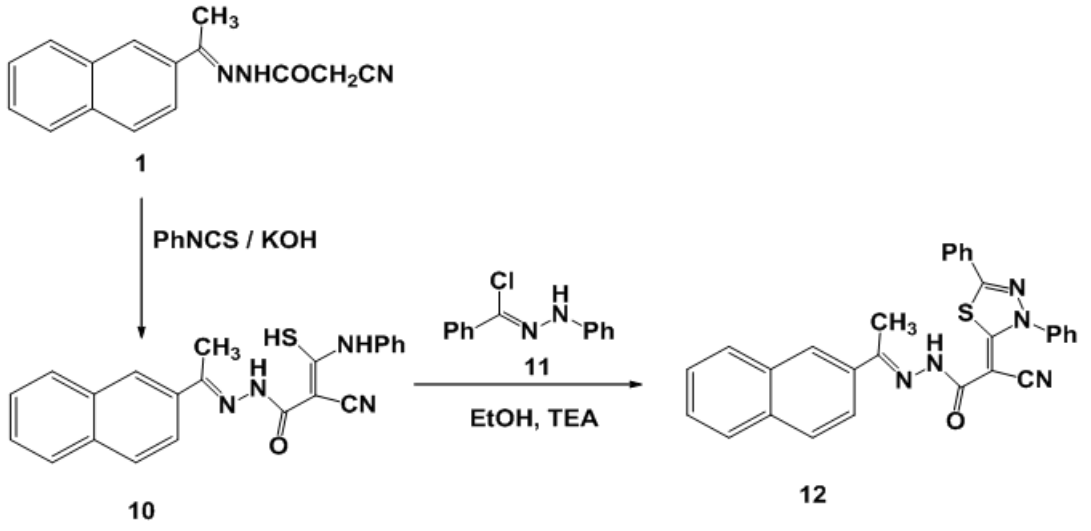
A considerable approach for the synthesis of 4, 6-dimethyl-1-((1-(naphthalen-2-yl)ethylidene)amino)-2-oxo-1,2-dihydropyridine-3-carbonitrile **7** was fullfiled through interaction of the hydrazone derivative **1** with acetylacetone in basic medium (scheme2); the product is formed as a result of acetylacetone tautomerization followed by loss of two molecules of water. In ^{1}HNMR spectrum of compound **7**, three characteristic singlet signals in the range 2.18-2.47 ppm attributable to the three methyl groups, also a nice singlet signal at 6.88 ppm, this is due to 3-H pyridine moiety, the mass spectrum showed a molecular ion peak in accordance with the proposed structure.

Furthermore, phenylisothiocyanate and sulfur could react with the target compound **1** in presence ot triethylamine to give finally the aminothiazolone derivative **8** through an addition protocol (scheme 2). Compound **8** in turnn was condensed with triethylorthoformate in acetic anhydride through loss of two ethanol molecules with amino function of **8** follwed by cyclization with NH function via loss of another ethanol molecule and furnished the thiazolopyrimidinone derivative **9** (scheme 2). Structure confirmation of both compounds **8** and **9** was assisted from their analytical and spectral data, for instance, IR spectrum of compound **8** displayed characteristic absorption bands at 3262, 3434 cm^{-1} related to NH_2 group as well as a carbonyl stretching vibration at 1617 cm^{-1}, in ^{1}HNMR spectrum, a signal integrating for two protons (NH_2) in the range 7.33-8.18 ppm along with aromatic protons and one exchangeable proton signal at 11.73 ppm for NH. Moreover, an EI mass spectroscopic technique gave its correct molecular ion peak at m/z = 418. Compound **9** showed a marked change in its spectral data, so that its IR displayed no absorption bands in the range of 3500-3100 cm^{-1} and so a complete disappearance of NH and NH_2 groups in the reaction course; more clearly, ^{1}HNMR spectrum no signals for exchangeable protons were present but a newly characteristic signal) in the range 7.33-8.13 ppm along with aromatic protons probably attributable to 2-H pyrimidinone ring.



Scheme 2

Thioanilides derivatives are important reactive isolable intermediate compounds which could be utilized in further heterocyclic synthesis; so that, we converted the target compound **1** into the corresponding thioanilide derivative **10**, this was accomplished by stirring equimolar amounts of compound **1** and phenylisothiocyanate in DMF containg potassium hydroxide for about 24 hours (scheme 3). The structure of the thioanilide **10** was established not only based on its elemental and spectral data (IR, mass) but also inferred from its reaction with hydrazonyl halide. The reaction of compound with hydrazonyl halide **11** was conducted in refluxing ethanol containing triethylamine and furnished 1,3,4-thiadiazoline derivative **12** (scheme 3) instead of the alternative thiazole derivative as reported by Hassaneen et.al. [22, 23] and also by Abunada [24], its mechanistic pathway was well reported before. Structure of compound **12** was inferred from its spectral data, so, mass spectrum gave a strong peak at m/z = 487 corresponding to its molecular weight; the ^{1}HNMR spectrum showed only one exchangeable proton signal at 10.42 ppm instead of three for compound **10**, also, the aromatic protons region was enriched by 5 protons.



Scheme 3

1.2. Antifungal screening

The antifungal screening data reveals that many of the newly synthesized compounds were active with moderate to good antifungal activity (Table 1). The compounds **3b, 3d, 3e, 8, 10** and **12** showed the highest activity towards all tested strains. The compounds **3a, 3c, 4, 6** and **7** showed good antifungal activity towards *Aspergillus fumigatus*, *Geotrichum candidum* and *Syncephalastrum racemosum*, and the compound **9** also showed potent activity towards *Candida albicans* and *Syncephalastrum racemosum*.

Table 1. Antifungal activity of the compounds 3a-e, 4, 6-10 and **12**

Compound	Minimal inhibitory concentration in µg/mL (zone of inhibition in mm)			
	Aspergillus fumigatus	*Geotrichum candidum*	*Candida albicans*	*Syncephalastrum racemosum*
3a	20 ± 0.11	18 ± 0.08	13 ± 0.20	18 ± 0.08
3b	23 ± 0.03	20 ± 0.11	16 ± 0.08	19 ± 0.14
3c	22 ± 0.09	19 ± 0.09	14 ± 0.21	19 ± 0.21
3d	22 ± 0.11	21 ± 0.05	17 ± 0.08	18 ± 0.09
3e	21 ± 0.08	20 ± 0.08	17 ± 0.11	17 ± 0.04
4	20 ± 0.08	18 ± 0.07	16 ± 0.21	16 ± 0.04
6	21 ± 0.03	19 ± 0.09	13 ± 0.07	17 ± 0.18
7	21 ± 0.15	20 ± 0.16	14 ± 0.21	18 ± 0.17
8	21 ± 0.09	20 ± 0.09	16 ± 0.08	19 ± 0.08
9	14 ± 0.11	12 ± 0.13	17 ± 0.17	17 ± 0.16
10	22 ± 0.08	21 ± 0.09	15 ± 0.06	18 ± 0.06
12	21 ± 0.05	20 ± 0.06	17 ± 0.09	18 ± 0.08
Clotrimazole	26 ± 0.11	23 ± 0.15	18 ± 0.18	20 ± 0.09

2. Experimental protocoals

2.1. Chemistry

Melting points were measured on Electrothermal IA 9000 series digital melting point apparatus. The IR spectra were recorded in potassium bromide discs on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometer. ^{1}H-NMR spectra was recorded in deuterated dimethyl sulfoxide (DMSO-*d*6) using a Varian Gemini 300 NMR spectrometer. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analysis was carried out at the Microanalytical Centre of Cairo University, Giza, Egypt. All reactions were followed by TLC (Silica gel, Merck). 2-Cyano-N'-(1-(naphthalen-2-yl)ethylidene)acetohydrazide [19] was prepared as reported in the literature.

2.1.1. Reaction of 1 with aromatic aldehydes 2a-e:

General procedure: To a solution of **1** (0.251 g, 1 mmol) and the appropriate aromatic benzaldehyde derivatives (1 mmol) in glacial acetic acid (20 mL), anhydrous sodium acetate (0.33 g, 4 mmol) was refluxed for 6h (monitored by TLC). The reaction mixture was left to cool and the formed solid was filtered off, washed with water, dried and recrystallized from DMF to give **3a-e**.

2-Cyano-N'-(1-(naphthalen-2-yl)ethylidene)-3-phenylacrylohydrazide (3a). Yield 78%; yellow solid; mp 126-8 ^{o}C; ^{1}H NMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 7.33-8.10 (m, 11H, ArH), 8.23 (s, 1H, =CH), 8.40 (s, 1H, Naphthalene-H1), 11.24 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1626 (C=O), 2214 (CN), 3442 (NH) cm^{-1}; MS m/z (%): 339(M^+, 100), 251(45), 184(47), 127(64), 77(87). Anal.Calcd for $C_{22}H_{17}N_3O$ (339.39): C, 77.86; H, 5.05; N, 12.38. Found C, 77.67; H, 5.01; N, 12.22%.

3-(4-Chlorophenyl)-2-cyano-N'-(1-(naphthalen-2-yl)ethylidene)acrylohydrazide (3b). Yield 76%; yellow solid; mp 120-2 ^{o}C; ^{1}H NMR (DMSO-d_6): δ 2.47 (s, 3H, CH_3), 7.39-8.19 (m, 10H, ArH), 8.28 (s, 1H, =CH), 8.40 (s, 1H, Naphthalene-H1), 11.23 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1622 (C=O), 2203 (CN), 3423 (NH) cm^{-1}; MS m/z (%): 373(M^+, 18), 251(29), 153(77), 127(100), 84(79). Anal. Calcd for $C_{22}H_{16}ClN_3O$ (373.83): C, 70.68; H, 4.31; N, 11.24. Found C, 70.55; H, 4.25; N, 11.16%.

2-Cyano-N'-(1-(naphthalen-2-yl)ethylidene)-3-(4-nitrophenyl)acrylohydrazide (3c). Yield 76%; yellow solid; mp 143-5 ^{o}C; ^{1}H NMR (DMSO-d_6): δ 2.45 (s, 3H, CH_3), 7.38-8.16 (m, 10H, ArH), 8.27 (s, 1H, =CH), 8.48 (s, 1H, Naphthalene-H1), 11.23 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1630 (C=O), 2211 (CN), 3434 (NH) cm^{-1}; MS m/z (%): 385(M^+ + 1, 5), 384(M^+, 11), 321(27), 276(27), 127(100), 84(78). Anal. Calcd for $C_{22}H_{16}N_4O_3$ (384.39): C, 68.74; H, 4.20; N, 14.58. Found C, 68.45; H, 4.12; N, 14.39%.

2-Cyano-3-(4-methoxyphenyl)-N'-(1-(naphthalen-2-yl)ethylidene)acrylohydrazide (3d). Yield 76%; yellow solid; mp 224 ^{o}C; ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 3.48 (s, 3H, OCH_3), 7.32-8.12 (m, 10H, ArH), 8.26 (s, 1H, =CH), 8.42 (s, 1H, Naphthalene-H1), 11.26 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1689 (C=O), 2216 (CN), 3444 (NH) cm^{-1}; MS m/z (%): 370(M^+ + 1, 7), 369(M^+, 9), 193(12), 153(37), 127(19), 55(100). Anal. Calcd for $C_{23}H_{19}N_3O_2$ (369.42): C, 74.78; H, 5.18; N, 11.37. Found C, 74.57; H, 5.13; N, 11.27%.

2-Cyano-3-(2,4-dichlorophenyl)-N'-(1-(naphthalen-2-yl)ethylidene)acrylohydrazide (3e). Yield 72%; yellow solid; mp 123-5 ^{o}C; ^{1}H NMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 7.39-8.17 (m, 9H, ArH), 8.29 (s, 1H, =CH), 8.48 (s, 1H, Naphthalene-H1), 11.27 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1614 (C=O), 2217 (CN), 3438 (NH) cm^{-1}; MS m/z (%): 409(M^+ + 1, 7), 408(M^+, 15), 340(12), 251(38), 153(100), 105(60). Anal. Calcd for $C_{22}H_{15}Cl_2N_3O$ (408.28): C, 64.72; H, 3.70; N, 10.29. Found C, 64.58; H, 3.48; N, 10.14 %.

2-Imino-N'-(1-(naphthalen-2-yl)ethylidene)-2*H*-chromene-3-carbohydrazide (6)

Yield 76%; yellow solid; mp 248 ^{o}C; ^{1}H NMR (DMSO-d_6): δ 2.49 (s, 3H, CH_3), 7.26-8.16 (m, 10H, ArH), 8.33 (s, 1H, Naphthalene-H1), 8.63 (s, 1H, Coumarine-H4), 9.31 (s, 1H, D_2O exchangeable, NH), 13.65 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1665 (C=O), 3217, 3438 (2NH) cm^{-1}; MS m/z (%): 356(M^+ + 1, 3), 355(M^+, 10), 183(58), 145(100). Anal. Calcd for $C_{22}H_{17}N_3O_2$ (355.39): C, 74.35; H, 4.82; N, 11.82. Found C, 74.42; H, 4.76; N, 11.56%.

2.1.2. Synthesis of 5-amino-N'-(1-(naphthalen-2-yl)ethylidene)-3-phenyl-1*H*-pyrazole-4-carbo-hydrazide (4)

A mixture of **3a** (0.339 g, 1 mmol) and hydrazine hydrate (0.50 g, 1 mmol) in absolute EtOH (50 mL) was refluxed for 4h (monitored by TLC). The reaction mixture was cooled and poured into cold water, the resulting precipitate was filtered off, washed with water, and recrystallized from dioxane to give **4**. Yield 68%; yellow solid; mp 212 ^{o}C; ^{1}H NMR (DMSO-d_6): δ 2.45 (s, 3H, CH_3), 7.28-8.19 (m, 13H, ArH and NH_2), 8.34 (s, 1H, Naphthalene-H1), 9.36 (s, 1H, D_2O exchangeable, NH), 11.86 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1648 (C=O), 3245, 3443 (NH_2, 2NH) cm^{-1}; MS m/z (%): 369(M^+, 37), 321(52), 240(24), 153(64), 84(100). Anal. Calcd for $C_{22}H_{19}N_5O$ (369.42): C, 71.53; H, 5.18; N, 18.96. Found C, 71.50; H, 5.12; N, 18.77%.

2.1.3. Synthesis of 4,6-dimethyl-1-((1-(naphthalen-2-yl)ethylidene)amino)-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (7)

A mixture of compound **1** (0.251 g, 1 mmol) and acetylacetone (0.10 g, 1 mmol) in ethanol (15 mL) containing a few drops of piperidine (3 drops) was refluxed for 10 h. The reaction mixture was cooled and the solid so obtained was filtered off and recrystallized from ethanol to give **7**. Yield 70%; white solid; mp 242-4 ^{o}C; ^{1}H NMR (DMSO-d_6): δ 2.18 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 6.88 (s, 1H, Pyridine-H_3), 7.23-8.18 (m, 6H, ArH), 8.34 (s, 1H, Naphthalene-H1); IR (KBr): ν_{max} 1645 (C=O), 2219 (CN) cm^{-1}; MS m/z (%): 315(M^+, 9), 300(100), 188(32), 127(87), 77(20). Anal. Calcd for $C_{20}H_{17}N_3O$ (315.37): C, 76.17; H, 5.43; N, 13.32. Found C, 76.12; H, 5.37; N, 13.26%.

2.1.4. Synthesis of 6-((1-(naphthalen-2-yl)ethylidene)amino)-3-phenyl-2-thioxo-2,3-dihydro thiazolo[4,5-d]pyrimidin-7(6*H*)-one (9)

I. Synthesis of 4-amino-N'-(1-(naphthalen-2-yl)ethylidene)-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carbohydrazide (8)

To a solution of compound **1**(0.251 g, 1 mmol) in ethanol (20 mL) containing triethylamine (0.25 mL), elemental sulfur (0.032 g, 1 mmol) and phenyl isothiocyanate (0.135 g, 1 mmol)

were added. The reaction mixture was heated at 60 ^{o}C for 2 h with continuous stirring and then poured into a beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration, dried, and recrystallized from DMF and ethanol (3:1) to give compound **8**. Yield 74%; yellow solid; mp 256 ^{o}C; ^{1}H NMR (DMSO-d_6): δ 2.48 (s, 3H, CH_3), 7.33-8.18 (m, 13H, ArH and NH_2), 8.42 (s, 1H, Naphthalene-H1), 11.73 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1617 (C=O), 3262, 3434 (NH_2 and NH) cm^{-1}; MS m/z (%): 419(M^++1, 13), 418(M^+, 37), 235(52), 154(76), 77(100). Anal. Calcd for $C_{22}H_{18}N_4OS_2$ (418.53): C, 63.13; H, 4.33; N, 13.39. Found C, 63.11; H, 4.26; N, 13.24%.

II. Reaction of 8 with $(EtO)_3CH$ / Ac_2O

A mixture of **8** (0.418 g, 1 mmol) and triethylorthoformate (0.148g, 1 mmol) in acetic anhydride (10 mL) was refluxed for 8h (monitored by TLC). The reaction mixture was cooled and poured into cold water, the resulting

precipitate was filtered off, washed with water, and recrystallized from DMF to give **9**. Yield 66%; yellow solid; mp 124-6 ºC; ^{1}H NMR (DMSO-d_6): δ 2.47 (s, 3H, CH_3), 7.33-8.13 (m, 12H, ArH and pyrimidine-H2), 8.52 (s, 1H, Naphthalene-H1); IR (KBr): ν_{max} 1630 (CO) cm^{-1}; MS m/z (%): 428(M$^+$, 100), 235(52), 154(56), 77(63). Anal. Calcd for $C_{23}H_{16}N_4OS_2$(428.53): C, 64.46; H, 3.76; N, 13.07. Found C, 64.43; H, 3.67; N, 12.87%.

2.1.5. Synthesis of 2-Cyano-3-mercapto-N'-(1-(naphthalen-2-yl)ethylidene)-3-(phenylamino) acrylohydrazide (10).

To a stirred solution of potassium hydroxide (0.56 g, 10 mmol) in dimethylformamide (30 mL) was add compound **1** (2.51 g, 10 mmol). After stirring for 30 minutes, phenyl isothiocyanate (1.35 g, 10 mmol) was added to the resulting mixture. Stirring was continued overnight. The reaction mixture was acidified with HCl and the solid product was filtered off, washed with water and dried. Recrystallization from ethanol gave pure **10** in 76% yield; yellow solid; mp 230 ^{o}C; ^{1}H NMR (DMSO-d_6): δ 2.48 (s, 3H, CH_3), 7.33-8.20 (m, 11H, ArH), 8.45 (s, 1H, Naphthalene-H1), 10.23 (s, 1H, D_2O-exchangeable, NH), 10.91 (s, 1H, D_2O exchangeable, NH), 12.28 (s, 1H, SH); IR (KBr): ν_{max} 1685 (C=O), 2217 (CN), 3436 (NH) cm^{-1}; MS m/z (%): 386 (M$^+$, 18), 188(54), 127(100), 77(67). Anal. Calcd for $C_{22}H_{18}N_4OS$ (386.47): C, 68.37; H, 4.69; N, 14.50. Found C, 68.31; H, 4.73; N, 14.43%.

2.1.6. Reaction of 10 with N'-phenylbenzohydrazonoyl chloride (11)

A mixture of **10** (0.386 g, 1 mmol) and N'-phenylbenzohydrazonoyl chloride **11** (0.230 g, 1mmol) in dioxane (30 mL) containing TEA (0.7 mL) was refluxed for 3h (monitored by TLC), allowed to cool and the solid formed was filtered off, washed with EtOH, dried and recrystallized from DMF to give 2-cyano-2-(3,5-diphenyl-1,3,4-thiadiazol-2(3H)-ylidene)-N'-(1-(naphthalen-2-yl)ethylidene)acetohydrazide **12.** Yield 73%; yellow solid; mp 266 °C; ^{1}H NMR (DMSO-d_6): δ 2.46 (s, 3H, CH_3), 7.25-8.16 (m, 16H, ArH), 8.39 (s, 1H, Naphthalene-H1), 10.42 (s, 1H, D_2O exchangeable, NH), IR (KBr): ν_{max} 1646 (C=O), 2212 (CN), 3430 (NH)cm^{-1}. MS m/z (%): 487 (M$^+$, 6), 351(100), 292(39), 127(21), 77(50). Anal. Calcd for $C_{29}H_{21}N_5OS$ (487.57): C, 71.44; H, 4.34; N, 14.36. Found C, 71.44; H, 4.34; N, 14.36%.

3.2. Antifungal activity assay

The newly synthesized target compounds 3a-e, 4, 6-10 and 12 were evaluated for their *in vitro* antifungal activity against *Aspergillus fumigatus* (AF), *Geotrichum candidum* (GC), *Candida albicans* (CA) and *Syncephalastrum racemosum* (SR) fungal strains. The organisms were tested against the activity of solutions of concentrations (5 mg/mL) and using inhibition zone diameter (IZD) in mm as criterion for the antimicrobial activity using agar diffusion well method [25].

The fungicides *Clotrimazole* was used as references to evaluate the potency of the tested compounds under the same conditions. The results are depicted in Table 1.

The microorganism inoculums were uniformly spread using sterile cotton swab on a sterile Petri dish Malt extract agar. One hundred μL of each sample was added to each well (10 mm diameter holes cut in the agar gel, 20 mm apart from one another). The systems were incubated for 24-48 h at 37 °C (for bacteria) and at 28 °C. After incubation, the microorganism's growth was observed. Inhibition of the fungal growth were measured as IZD in mm. tests were performed in triplicate.

4. Conclusions

2-Cyano-N'-(1-(naphthalen-2-yl)ethylidene)acetohydrazide was utilized as key intermediate for the synthesis of some new heterocycles, namely 1,2-dihydropyridine, 2,3-dihydrothiazole, 2,3-dihydrothiazolo[4,5-d]pyrimidinone, thiadiazole, pyrazole and pyrazolo[3,4-d]pyrimidinone.

All the synthesized compounds were tested for *in vitro* activities against certain strains of fungi, among them, the compounds **3b**, **3d**, **3e**, **8**, **10** and **12** exhibited potent inhibitory activity towards all tested fungi.

References

1. Rollas, S., Kalyoncuoğlu, N., Sur-Altiner, D. and Ye-ğenoğlu, Y. (1993): 5-(4-Aminophenyl)-4-substituted-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones: Synthesis and antibacterial and antifungal activities. *Pharmazie*, 48(4): 308-309.

2. Papakonstantinou-Garoufalias, S., Pouli, N., Marakos, P. and Chytyro-glouladas, A. (2002): Synthesis Antimicrobial and antifungal activity of some new 3-substituted derivatives of 4-(2,4-dichlorophenyl)-5-adamantyl)-1*H*-1,2,4-triazole. *Il Farmaco*, 57(12): 973-977.

3. Kidwai, M., Kumar, R., Srivastava, A. and Gupta, H. P. (1998): Microwave-assisted synthesis of novel 1,3,4-thiadiazolyl-substituted 1,2,4-triazines as potential antitubercular agents. *Bioorg. Med. Chem.* 26(5): 289-294.

4. Kachhadia, V. V., Patel, M. R. and Joshi, H. S. (2005): Heterocyclic systems containing S/N regioselective nucleohilic competition: Facile synthesis, antitubercular and antimicrobial activity of thiohyydantoins and iminothiazolidinones containing the benzo[b]thiophene moiety. *J. Serb. Chem. Soc.*, 70(2): 153-161.

5. Kadaba, P. K. (2003): Rational drug design and the discovery of the delta 2-1,2,3-triazolines, a unique class of anticonvulsant and antiischemic agents. *Curr. Med. Chem.*, 10(20): 2081-2108.

6. küçükgüzel, İ., Küçükgüzel, Ş. G., Rollas, S., Ö.-Saniş, G., Özdemir, O., Bayrak, I., Altuğ T. and Stables, J. P. (2004): Synthesis of some 3-(arylalkylthio)-4-alkyl/aryl-5-(4-amino- phenyl)-4*H*-1,2,4-triazole derivatives and their anticonvulsant activity. *Il Farmaco*, 59(11): 893-901.

7. Mullican, M. D., Wilson, M. W., Connor, D. T., Kostlan, C. R., Schrier, D. J. and Dyer, R. D. (1993): Design of 5-(3,5- di-tert-butyl-4-hydroxyl-phenyl)-1,3,4-thiadiazoles, -1,3,4-oxadiazoles, and -1,2,4-triazoles as orally-active, non- ulcerogenic antiinflammatory agents. *J. Med. Chem.*, 36(8): 1090-1099.

8. Palaska, E., Şahin, G., Kelicen, P., Durlu, N. T. and Altinok, G. (2002): Synthesis and anti-inflammatory activity of 1-acylthiosemicarb-azides, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazole-3-thiones. *Il Farmaco*, 57(2): 101-107.

9. Varvaresou, A., Siatra-Papastaikoudi, T., Tsotinis, A., TsantiliKakoulidou A. and Vamvakides, A. (1989): Synthesis, lipophilicity and biological evaluation of indole-containing derivatives of 1,3,4-thiadiazole and 1,2,4-triazole. *Il Farmaco*, 53(5): 320-326.

10. Holla, B. S., Veerendra, B., Shivanada M. K. and Poojary, B. (2003): Synthesis characterization and anticancer activity studies on some Mannich bases derived from 1,2,4- triazoles. *Eur. J. Med. Chem.*, 38(7): 759-767.

11. Lange, J. H., Stuivenberg, H. H., Coolen, H. K., Adolfs, T. J., McCreary, A. C., Keizer, H. G., Wals, H. C., Veerman, W., Borst, A. J., de Looff, W., Verveer, P. C. and Kruse, C. G. (2005): Bioisosteric replacements of the pyrazole moiety of rimonabant: synthesis, biological properties, and molecular modeling investigations of thiazoles, triazoles, and imidazoles as potent and selective CB1 cannabinoid receptor antagonists. *J. Med. Chem.*, 48(6): 1823-1838.

12. Kastron, V. V., Duburs, G., Vitolins, R., Skrastins, I., Kimenis, A. A. (1985): Synthesis and pharmacological activity of 4-(2-difluoromethoxyphenyl)-1,4-dihydropyridines. *Khim. Farm. Zh.*, 19: 545-549.

13. Quintela, J. M., Peinador, C., Botana, L., Estevez, M., Reiguera, R. (1997): Synthesis and antihistaminic activity of 2-guanadino-3-cyanopyridines and pyrido[2,3-d]-pyrimidines. *Bioorg. Med. Chem.*, 5: 1543-1553.

14. Toyota, K., Shinkai, H., Etou, H., Kamimura, A., Eguchi, C., Oosumi, K., Turuo, T. (Ajinomoto Co., Inc.; Japanese Foundation for Cancer Research) Eur. Pat. Appl. EP 330,470 (Cl. C07D211/90) 30 Aug. 1989; Chem. Abstr. 112, 158059 (1990).

15. Gorlitzer, K., Klanck, S. (1999): Metronidazole derivatives with intramolecular equivalents of reduction. *Pharmazie*, 54: 814-819.

16. Badr, M. Z. A., Mahgoub, S. A., Abdel-Latif, F. F., Abd El-Hafez, A. A. A. (1991): Synthesis and reactions of some new thieno[2,3-b]-pyridines and the antimicrobial effects. *Phosphorus, Sulfur Silicon Relat. Elem.*, 55: 175-183.

17. Hishmat, O. H., Abdel Galil, F. M., Farrag, D. S. (1990): Synthesis and antimicrobial activity of new benzofuranylpyridine derivatives. *Pharmazie*, 45: 793-795.

18. Schubert, J., Wild, J., Harreus, A., Kuekenhoehner, T., Sauter, H., Ammermann, E., Lorenz, G. (BASF A.-G.)Ger. Offen. DE 3,905, 238 (Cl. C07D213/84) 23 Aug.1990; Chem. Abstr. 114, 101740 (1991).

19. Abd El Aziz, H. M., Gomha, S. M. (2013): Synthesis and *in vitro* anti-breast cancer activity of some novel 1,4-dihydropyridine derivatives. *Int. J. Pharm. Pharm. Sci*. *5*(3): 183-9.

20. Brahmbhatt, D. I., Shashibala, S. and Patel, K. C. (1999): Characterization and biological activity of somepolycoumarin ethylenes. *Eur. Polymer J*., 35: 317–324.

21. Chodankar, N. K. and Seshadri, S. (1984): Absorption-emission spectra studies of 3-hetarylcoumarin. *Dyes Pigments*, 6: 331-340.

22. Hassaneen, H. M., Harhash, A. E., Abunada, N. M., Abdallah, T. A. and Algharib, M. S. (1993): Cyano-(1-methylbenzimidazol-2-yl)thiazole derivatives. *J. Chem. Research* (*S*), 194-195.

23. Hassaneen, H.M., Elwan, N.M., Abdelhadi, H.A. and Abdallah, T.A. (1995): Reactions of thioanilides with active chloromethylene compounds. Synthesis of 1, 3- oxathiol-2-ylidene derivatives. *Sulfur Lett*., 18: 121-128.

24. Abu Nada, N. (2007): Synthesis of 2-(isoquinolinemethylidene)-1,3,4-thiadiazole derivatives. *J. Al-Aqsa Unv*., 11: 12-21.

25. Smania, A. Monache, F. D. Smania, E. F. A. and R.S. (1999): Cuneo. Triterpenes and sterols from ganoderma australe (Fr.) Pat. (Aphyllophoromycetideae). *Int. J. Med. Mushrooms*, 1: 325-334.