SYNTHESIS AND ANTIFUNGAL TESTING OF SOME NEW TRICYCLIC HETEROCYCLIC QUINOLINES

Ali A.Abdel Hafez* and Nariman M.Nahas**
* Department of Chemistry, Faculty of Science, Assiut University, Assiut-Egypt.
** Deparment of Chemistry, Faculty of Applied Science, Umm Al-Qura University, Makkah, P.O. Box 16222, Saudi Arabia.

Abstract: New 2-amino-4-aryl-3-(4,5-dihydro-1H-imidazol-2-yl)pyrano[3,2-h]quinolines have been prepared. Their cyclization with triethyl orthoformate, aldehyde, ketone and carbon disulfide afforded the corresponding imidazo[1,2-c]pyrimido[4,5:6,5]pyrano[3,2-h]quinolines. Also, a series of polycyclic heterocyclic containing condensed triazol and triazines have been prepared by cyclization of the hydrazino derivatives with formic acid and carbon disulfide (Scheme-1). Antifungal tests were also performed.

Introduction

The pyran ring system is an interesting class of heterocycles. It has been reported that pyran derivatives exhibit antimicrobial activities(1), growth stimulating effects(2), antifungal and plant growth regulation effects(3), antitumor activity(4), central nervous system activity(5) and hypotensive effect(6). On the other hand, fused pyrimidines were found to possess a wide biological activities such as antimicrobial(7.8), antiparkinsonian(9), leishmanicidal and herbicidal(10) effect. Morever, quinoline derivatives have found useful application antimicrobial(11), antimalarial(12), cardiovascular and biochemically active compounds(13). In addition to the previously mentioned properties, many imidazoles and triazines are used as therapeutic tools(14-16). As a continuation of our previous work(17-21) and considering the particular interest inherent in the above mentioned properties, we aimed to synthesize the title compounds in the hope that members of thom would find interesting biological applications.

Experimental

All melting points are uncorrected. IR (γ, cm^{-1}) spectra were recorded on Nicolet Jeol 205 FTIR. NMR spectra were reconded on an EM-360-200 MH_z spectrometers in suitable deuterated solvent using TMS as an internal standard. Mass spectra were recorded on a Jeol JMS 600 instrument. Elemental analysis were determined on a Perkin Elmer 240 microanalyser.

2- Amino –4-aryl-3(4,5 dihydro-1H-imidazol-2-yl)pyrano[3,2-h]quinolines(2a-e)

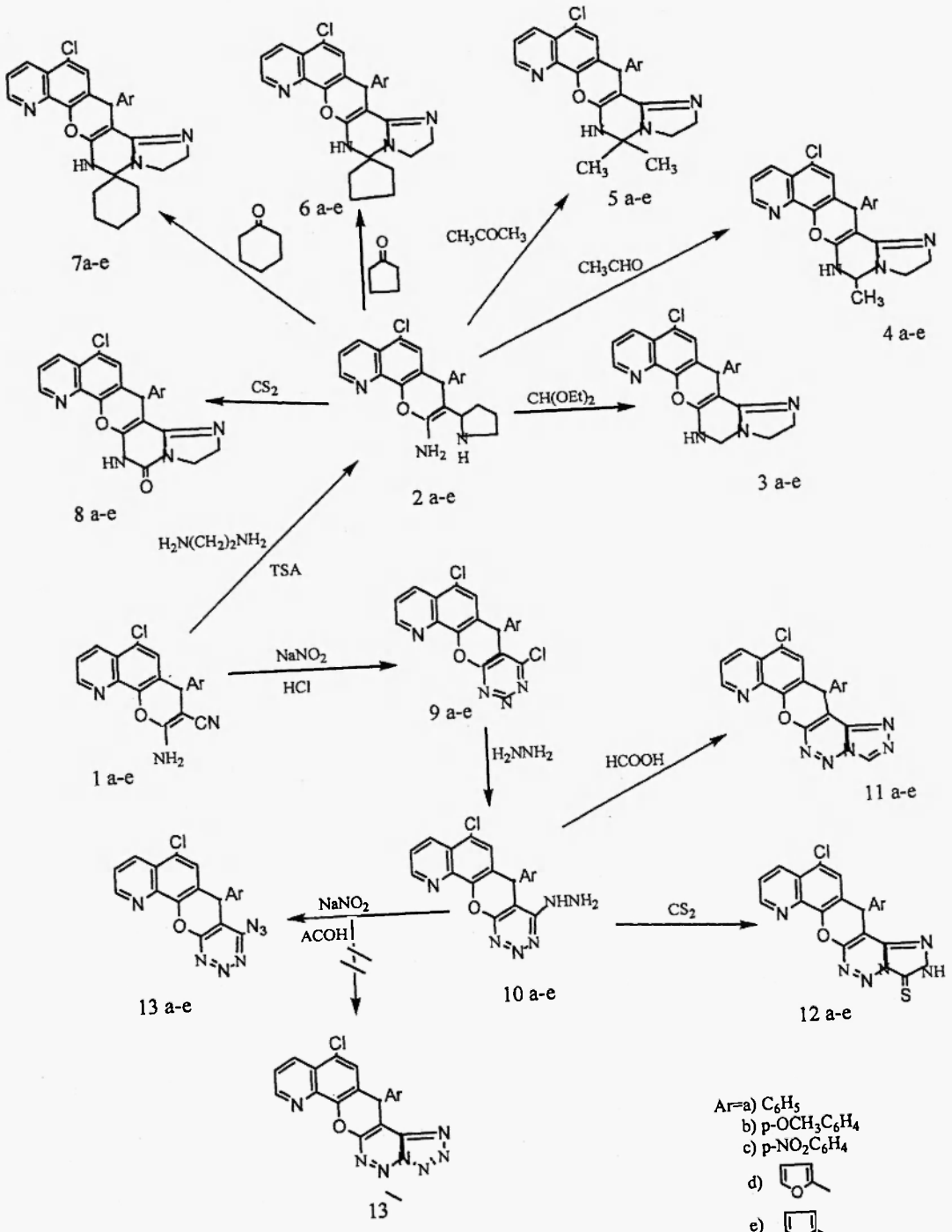
General Procedure :

A mixture of 1_{a-e} (0.01 mol), ethylenediamine (0.01mol) and p.toluensulfonic acid monohydrate (0.012mol) was heated under reflux for 12h. The reaction mixture was made alkaline with a saturated aqueous solution of sodium carbonate and the preciptate was filtered off and recrystallized from proper solvent.

2,3-Dihydroimidazo[1,2-c]pyrimido[4',5':6,5]pyrano[3,2-h]quinolines(3_{a-e})

General Procedure :

To a suspension of 2_{a-e} (0.01 mol) in triethyl orthoformate (0.018 mol), was added small of formic acid (0.5 ml), the mixture was heated under reflux for 7h. After cooling to rt the product was collected by filtration and recrystallized from proper solvent.



7a-e 6 a-e 5 a-e 4 a-e 8 a-e 2 a-e 3 a-e 1 a-e 9 a-e 11 a-e 13 a-e 10 a-e 12 a-e 13

Scheme 1

2,3,6-Trihydroimidazo[1,2-c]pyrimido[4',5':6,5]pyrano[3,2-h]quinolines(4_{a-e}, 7_{a-e})
General Procedure :
To a solution of 2_{a-e} (0.01 mol) and the appropriat aldehyde (0.011 mol) or ketone (0.02 mol) in absolute ethanol (30 ml) was added, the mixture was stirred at 80-100°C in a well stoppered round bottom flask fitted with reflux condenser for 12h. The product was isolated by column chromotograph on scilica gel with ethyl acetate / methanol/aq. NH_3(6:2:2) as eluent.

5-Thioxo-2,3,6-trihydroimidazo[1,2-c]pyrimido[4',5':6,5]pyrano[3,2-h]quinolines(8_{a-e})
General Procedure :
A mixture of 2_{a-e} (0.001 mol), carbon disulfide (5 ml) in ethanol (50 ml) and two pellets of potassium hydroxide (0.17 g, 0.003 mol) was heated under reflux on water bath for 6h. The solid product obtained was dissolved in water and then acidified with acetic acid and recrystallized from diluted acetic acid.

5-Aryl-4,7-dichloro[1,2,3]triazino[4',5':6,5]pyrano[3,2-h]quinolines(9_{a-e})
General Procedure :
To an ice cold solution of 1_{a-e} (0.01 mol) in a mixture of acetic acid (20 ml) and hydrochloric acid (10 ml), sodium nitrite (0.01 mol in 10 ml H_2O) was added with stirring for 30 min. and the stirring was continued for 3h. The product was collected and recrystallized from diluted acetic acid.

5-Aryl-7-chloro-4-hydrazino[1,2,3]triazino[4',5':6,5]pyrano[3,2-h]quinolines(10_{a-e})
General Procedure :
A mixture of 9_{a-e} (0.002 mol) and hydrazine hydrate (2 ml, 98%) in ethanol (30 ml) was heated under reflux for 6h. The product obtained after cooling was filtered off, washed with water and recrystallized from ethanol.

14-Aryl-12-chloro[1,2,4]triazolo[3,4-f][1,2,3]triazino[4',5':6,5]pyrano[3,2-h]quinolines(11a-e).
General Procedure :
A mixture of 10a-e (0.001 mol) in formic acid (20 ml) was heated under reflux for 8 hr. The reaction mixture was concentrated in vacuo and the solid product was collected, washed with water and recrystallized from methanol.

14-Aryl-12-chloro-3-thioxo[1,2,4]triazolo[3,4-f][1,2,3]triazino[4',5':6,5]pyrano [3,2-h]quinolines(12a-e).
General Procedure :
A mixture of 10a-e (0.001 mol) , carbon disulfide (5 ml) in ethanol (50 ml) and two pellets of potassium hydroxide was heated under reflux for 6 hr. The solid product obtained was dissolved in water and then acidified with acetic acid and recrystallized from diluted acetic acid.

5-Aryl-4-azido-7-chloro[1,2,3]triazino[4',5':6,5]pyrano[3,2-h]quinolines(13a-e).
General Procedure :
To a well-stirred solution of 10a-e (0.002 mol) in glacial acetic acid (50 ml), a solution of sodium nitrite (1 g in 10 ml water) was add at rt and stirring was contiued for 1hr. The solid obtained was filtered off, washed with water and recrystallized from acetic acid.

Results and Discussions

2-Amino-4-aryl-3(4,5-dihydro-1H-imidazo-2-yl)pyrano[3,2-h]quinolines (2a-e) were prepared by the reaction of the pyranoquinolines 1a-e with ethylenediamine, which serve as intermediate for the synthesis of imidazo[1,2-c]pyrimido[4',5' : 6,5]pyrano[3,2-h]quinolines.

Thus the reaction of compounds 2a-e with triethyl orthoformate, aldehydes and ketones gave the corresponding2,3-dihydroimidazo[1,2-c]pyrimido[4',5':6,5]pyrano[3,2-h]quinolines (3_{a-e}) and 2,3,6-trihydroimidazo[1,2-c]pyrimido[4',5':6,5]pyrano[3,2-h]quinolines(4_{a-e}-5_{a-e}), while the reaction with cyclic ketones and carbon disulfide gave spiroimidazo[1,2-c]pyrimido[4',5':6,5]pyrano[3,2-

h]quinolines(6_{a-c}-7_{a-c}) and 5-thioxo-2,3,6-trihydroimidazo[1,2-c]pyrimido[4',5':6,5] pyrano[3,2-h]quinolines (8_{a-c}) respectively. The chlorine atom reactivity at C-4 of 9_{a-c} was highlighted by its easy displacement with nucleophilic reagent as hydrazine hydrate to give the hydrazino derivative 10_{a-c} which in turn, proved to be a useful intermediate.

In fact, the triazino derivatives 11a-e ande 12a-e were produced from the reaction of 10a-e with formic acid and carbon disulphide, respectively.

In addition, treatment of 10a-e in acetic acid and an aqueaus solution of sodium nitrite, at room temperature gave the azido derivatives 13_{a-c}, the structure of which was assigned on the basis of its IR spectra (N_3 stretching at 2140 cm^{-1}), this ruling out the alternative tetrazol structure 13'. All the newly synthesized compounds were tested against three species of fungi, namely, Aspergillin flavies, Aspergillus niger and Penicillium chrysogenum and the data are listed in (Table 2).

Conclusions

This work reports a facil method for the synthesis of tricyclic heterocyclic quinolines as antifungal agents.

Table-1: Physical data of the newly synthesized compounds 2a-e-13a-e

Compd. No.	Yield %	Mp (°C)	Molecular Formula	IR (γ,cm^{-1}) (KBr)and MS	NMR (δ,ppm) (solvent)	Anal.Calcd/(Found) %				
						C	H	N	S	Cl
2a	62	180-82	$C_{21}H_{17}N4OCl$ (Methanol)	3288-3073(NH_2) ,3430 (NH), m/z 376	($CDCl_3$):4.95(s,1H, pyran),6.60(s,2H,NH_2), 8.95(s,1H,NH),3.30 (t,2H,CH_2,j=6.4Hz),3.90 (t,2H,CH_2,j=6.4Hz), 700-8.45 cm,9H,arom.	66.92 (66.78)	4.55 (4.48)	14.87 (14.95)	- -	9.42 (9.35)
2b	68	161-163	$C_{22}H_{19}N_4O_2Cl$ (Dioxane)	3440-3340(NH_2), 3320 (NH)	(CF_3COOD):5.00(s,1H, pyran),3.35(t,2H,CH_2, j=6.4Hz),3.80(t,2H,CH_2, 6.4Hz),2.30(s,3H,CH_3), 6.90-8.30(m,8H,arom)	64.93 (64.85)	4.70 (4.66)	13.77 (13.85)	- -	8.72 (8.64)
2c	74	146-148	$C_{21}H_{16}N_5O_3Cl$ (Methanol)	3350-3211(NH_2), 3452(NH)	($CDCl_3$):5.00(s,1H, pyran),3.40(t,2H,CH_2, j=6.4Hz),3.80(t,2H,CH_2, j=6.4Hz),6.70(s,2H, NH_2),9.00(s,1H,NH), 7.00-8.40(m,8H,arom.)	59.78 (59.87)	3.82 (3.87)	16.60 (16.54)	- -	8.42 (8.48)
2d	78	>300	$C_{19}H_{13}N_4O_2Cl$ (Ethanol)	3340-3240(NH_2), 3320(NH)	(CF_3COOD):5.00(s,1H, pyran),3.40(t,2H,CH_2, j=6.4Hz),3.80(t,2H,CH_2, j=6.4Hz),7.00-8.30(m, 7H,arom)	62.20 (62.31)	4.12 (4.21)	15.28 (15.19)	- -	9.68 (9.79)
2e	71	206-208	$C_{19}H_{15}N_4OSCl$ (Dioxane)	3216-3052(NH_2), 3320(NH)	(CF_3COOD):4.90(s,1H, pyran),3.40(t,2H,CH_2, j=6.4Hz),3.80(t,2H,CH_2, j=6.4Hz),2.30(s,3H, CH_3),7.00-8.40(m,7H, Arom)	59.59 (59.47)	3.95 (3.87)	14.63 (14.71)	8.38 (8.47)	9.27 (9.36)
3a	58	295-297	$C_{22}H_{15}N_4OCl$ (Dioxane)	3058(CHarom.) m/z 386	($CDCl_3$):4.95(s,1H, pyran),3.90-4.05(m,4H, $2CH_2$),7.10-8.50(m,9H, arom.)	68.30 (68.18)	3.91 (3.85)	14.49 (14.37)	- -	9.18 (9.25)

Table-1 (continued): Physical data of the newly synthesized compounds 2a-e-13a-e

3b	65	241-243	$C_{23}H_{17}N_4O_2Cl$ (Ethanol)	3058(CH arom.), 12930-2832 (CH aliph.)	($CDCl_3$):5.00(s,1H, pyran),2.40(s,3H, CH_3),3.80-4.00(m,4H, $2CH_2$)7.00-8.40(m,8H, arom.)	66.26 (66.39)	4.11 (4.18)	13.44 (13.37)	- -	8.25 (8.46)
3c	70	255-257	$C_{22}H_{14}N_5O_3Cl$ (Ethanol)	3037(CH. arom.), 2923-2848	($CDCl_3$):5.00(s,1H, pyran),3.90-4.00(m,4H, $2CH_2$)7.00-8.35(m,8H, arom.)	61.18 (61.31)	3.27 (3.31)	16.22 (16.36)	- -	8.22 (8.31)
3d	73	>300	$C_{20}H_{13}N_4O_2Cl$ (Ethanol)	3052(CH arom.), 2937(CH aliph.)	($CDCl_3$):5.00(s,1H, pyran),3.80-3.95(m,4H, $2CH_2$)6.85-8.10(m,7H, arom.)	63.74 (63.58)	3.48 (3.57)	14.87 (14.96)	- -	9.42 (9.55)
3e	67	248-250	$C_{20}H_{13}N_4OSCl$ (methanol)	3042(CHarom), 2930(CH aliph.)	($CDCl_3$):5.00(s,1H, pyran),3.80-3.95(m,4H, $2CH_2$)6.80-8.00(m,7H, arom.)	61.13 (61.28)	3.34 (3.41)	14.26 (14.11)	8.17 (8.26)	9.04 (9.18)
4a	35	>300	$C_{23}H_{19}N_4OCl$ (methanol)	3380 (NH)	($CDCl_3$):2.10(d,3H,CH_3),3.50-3.90(m,4H,$2CH_2$) 5.00(s,1H,pyran),5.50 (m,1H,CH),6.60(s,1H, NH)7.10-8.85(m,9H, Arom.)	68.56 (68.45)	4.75 (4.66)	13.91 (13.80	- -	8.81 (8.72)
4b	31	222-224	$C_{24}H_{21}N_4O_2Cl$ (dioxane)	2960-2919(CH aliph.), 3400(NH) (dioxane)	($CDCl_3$):2.00(d,3H, CH_3),2.20(s,3H,CH_3),3. 50-3.90(m,4H,$2CH_2$), 5.00(s,1H,pyran),5.45 (m,1H,CH),6.60(s,1H, NH),7.108.80(m,8H, arom.)	66.58 (66.71)	4.89 (4.78)	12.49 (12.81)	- -	8.20 (8.31)
4c	36	240-242	$C_{23}H_{18}N_5O_3Cl$	3430 (NH)	($CDCl_3$):2.00(d,3H, CH_3),3.50-3.80(m,4H, $2CH_2$),5.00(s,1H,pyran), 5.50(m,1H,CH),6.60(s, 1H,NH)7.10-8.80(m, 8H.arom.)	61.67 (61.53)	4.05 (4.13)	15.64 (15.51)	- -	7.93 (7.85)
4d	39	>300	$C_{21}H_{17}N_4O_2Cl$ (dioxane)	3900 (NH)	($CDCl_3$):2.00(d,3H, CH_3),3.50-3.90(m,4H, $2CH_2$),5.00(s,1H,pyran), 5.40(m,1H,CH),6.50 (s,1H,NH)6.80-8.50(m, 7H.arom.)	64.19 (64.31)	4.36 (4.43)	14.26 (14.14)	- -	9.04 (9.13)
4e	41	>300	$C_{21}H_{17}N_4OSCl$ (dioxane)	3400(NH) m/z 409,	($CDCl_3$):2.00(d,3H, CH_3),3.50-3.80(m,4H, $2CH_2$),5.00(s,1H,pyran), 5.50(m,1H,CH),6.50 (s,1H,NH),6.70-8.60(m, 7H.arom.)	61.67 (61.53)	4.19 (4.25)	13.70 (13.84)	7.85 (7.71)	8.68 (8.570
5a	43	>300	$C_{24}H_{21}N_4OCl$	3359(NH),3063 (CH arom.),2966 (CH aliph.)	($CDCl_3$):2.90(s,6H, $2CH_3$),3.4-3.70(m,4H, $2CH_2$),5.00(s,1H,pyran), 6.70(s,1H,NH),7.10-8.60(m,9H,arom.)	69.13 (69.29)	5.08 (5.19)	13.44 (13.56)	- -	8.15 (8.63)
5b	39	>300	$C_{25}H_{23}N_4O_2Cl$	3365(NH),3037 (CH arom.),2930-2822(CH aliph.)	($CDCl_3$):2.20(s,3H,CH_3) ,2.90(s,6H,2CH3),3.40-3.80(m,4H,2CH2), 5.00(s,1H,pyran),6.60(s, 1H,NH),7.00-8.60(m, 8H.arom.)	67.18 (67.32)	5.19 (5.26)	12.54 (12.41)	- -	7.94 (7.85)
5c	34	>300	$C_{24}H_{20}N_5O_3Cl$	3380(NH),2969 (CH aliph.)	($CDCl_3$):2.90(s,6H, $2CH_3$),3.40-3.80(m,4H, $2CH_2$),5.00(s,1H,pyran), 6.60(s,1H,NH),7.00-8.50(m,8H,arom.)	62.40 (62.29)	4.36 (4.47)	15.16 (15.05)	- -	7.69 (7.58)

Table-1 (continued): Physical data of the newly synthesized compounds 2a-e-13a-e

5d	30	290-292	$C_{22}H_{19}N_4O_2Cl$	3400(NH),2919 (CH aliph.)	($CDCl_3$):2.80(s,6H, $2CH_3$),3.40-3.75(m,4H, $2CH_2$),5.00(s,1H,pyran), 6.50(s,1H,NH)6.80-8.30 (m,7H,arom.)	64.93 (64.78)	4.71 (4.61)	13.77 (13.63)	- -	8.72 (8.60)
5e	32	246-248	$C_{22}H_{19}N_4OSCl$	3400(NH),m/z 423	($CDCl_3$):2.80(s,6H, $2CH_3$),3.40-3.75(m,4H, $2CH_2$),5.00(s,1H,pyran), 6.50(s,1H,NH),6.80-8.20(m,7H,arom.)	62.46 (62.59)	4.53 (4.42)	13.25 (13.38)	7.39 (7.46)	9.39 (9.26)
6a	58	196-198	$C_{26}H_{23}N_4OCl$	3380(NH),2961-2863(CH aliph.)	($CDCl_3$):1.40-1.80(m, 8H,cyclopentane), 3.70-4.05(m,4H,$2CH_2$), 5.00(s,1H,pyran),6.50(s, 1H,NH),7.10-8.70(m, 9H,arom.)	70.49 (70.38)	5.23 (5.32)	12.65 (12.76)	- -	8.01 (8.13)
6b	55	>300	$C_{27}H_{25}N_4O_2Cl$	3365(NH), m/z 473	($CDCl_3$):1.40-1.80(m, 8H,cyclopentane),2.20 (s,3H,CH_3),3.70-4.50(m,4H,$2CH_2$), 5.00(s,1H,pyran),5.50 (m,1H,CH),6.50(s,1H, NH),7.00-8.60(m,8H, arom.)	68.56 (68.42)	5.33 (5.41)	11.85 (11.73)	- -	7.51 (7.69)
6c	60	248-250	$C_{26}H_{22}N_5O_3Cl$	3467(NH),3053 (CH arom.),2925 (CH aliph.),m/z 488	($CDCl_3$):1.50-1.90(m, 8H,cyclopentane),3.80-4.10(m,4H,$2CH_2$), 5.00(s,1H,pyran),6.60(s, 1H,NH),7.10-8.70(m, 8H,arom.)	63.99 (63.84)	4.54 (4 61)	14.36 (14.45)	- -	7.28 (7.39)
6d	56	>300	$C_{24}H_{21}N_4O_2Cl$	3396(NH),2950 (CH aliph.)	($CDCl_3$):1.40-1.80(m, 8H,cyclopentane),3.70-4.00(m,4H,$2CH_2$), 5.00(s,1H,pyran),6.50(s, 1H,NH),6.80-8.40(m, 7H,arom.)	66.58 (66.42)	4.89 (4.97)	12.64 (12.79)	- -	8.20 (8.36)
6e	59	>300	$C_{26}H_{23}N_5OSCl$	3406(NH),m/z 449	($CDCl_3$):1.40-1.80(m, 8H,cyclopentane),3.70-4.00(m,4H,$2CH_2$), 5.00(s,1H,pyran),6.50(s, 1H,NH),6.80-8.50(m, 7H,arom.)	64.19 (64.36)	4.71 (4.64)	12.48 (12.33)	7.15 (7.27)	7.91 (7.82)
7a	56	>300	$C_{27}H_{25}NOCl$	3424(NH),m/z 457	($CDCl_3$):1.40-1.80(m, 10H,cyclohexane),3.80-4.20,(m,4H,$2CH_2$), 4.95(s,1H,pyran), 6.60(s,1H,NH),7.10-8.50(m,9H,arom.)	70.79 (70.82)	5.51 (5.43)	12.26 (12.17)	- -	7.77 (7.82)
7b	59	>300	$C_{28}H_{27}N_2O_2Cl$	3375(NH),m/z 487	($CDCl_3$):1.40-1.80(m, 10H,cyclohexane),2.30 (s,3H,CH_3),3.90-4.10 (m,4H,$2CH_2$),5.00(s, 1H,pyran),6.70(s,1H,NH),7.10-8.60(m,8H, arom.)	69.05 (69.18)	5.59 (5.65)	11.51 (11.38)	- -	7.29 (7.18)
7c	60	176-178	$C_{27}H_{24}N_5O_3Cl$	3339(NH),2930-2858(CH aliph.)	($CDCl_3$):1.50-1.90(m, 10H,cyclohexane),3.90-4.10,(m,4H,$2CH_2$), 5.00(s,1H,pyran), 6.70(s,1H,NH),7.10-8.60(m,8H,arom.)	64.59 (64.43)	4.82 (4.74)	13.95 (13.80)	- -	7.07 (7.19)
7d	63	>300	$C_{25}H_{21}N_4O_2Cl$	3391(NH),2930 (CH aliph.)	($CDCl_3$):1.50-1.80(m, 10H,cyclohexane),3.80-4.00,(m,4H,$2CH_2$), 5.00(s,1H,pyran), 6.60(s,1H,NH),6.80-8.40(m,7H,arom.)	67.18 (67.30)	5.19 (5.28)	12.54 (12.41)	- -	7.94 (7.82)

Table-1 (continued): Physical data of the newly synthesized compounds 2a-e-13a-e

7e	61	>300	$C_{25}H_{23}N_4OSCl$	3380(NH),2930 (CH aliph.)	($CDCl_3$):1.50-1.80(m, 10H,cyclohexane),3.80-4.00,(m,4H,$2CH_2$), 5.00(s,1H,pyran), 6.60(s,1H,NH),6.80-8.40(m,7H,arom.)	64.84 (64.69)	5.01 (5.12)	12.10 (12.25)	6.93 (6.81)	7.67 (7.78)
8a	63	>300	$C_{22}H_{15}N_4OSCl$	3432(NH),3058 (CH arom.)	(CF_3COOD):3.70-3.90 (m,4H,$2CH_2$),4.90(s,1H, pyran)	63.06 (63.17)	3.61 (3.50)	13.38 (13.25)	7.66 (7.52)	8.47 (8.35)
8b	61	200-202	$C_{23}H_{17}N_4O_2SCl$	3375(NH),3058 (CH arom.),2930-2822(CH aliph.), m/z 449	(CF_3COOD):2.25(s,3H, CH_3),3.70-3.90(m,4H, $2CH_2$),5.00(s,1H,pyran), 7.00-8.50(m,8H,arom.)	61.52 (61.64)	3.82 (3.74)	12.48 (12.33)	7.15 (7.29)	7.91 (7.75)
8c	67	238-240	$C_{22}H_{14}N_5O_3SCl$	3350(NH),3063 (CH arom.),2920 (CH aliph.)	(CF_3COOD):3.80-4.00 (m,4H,$2CH_2$),5.00(s,1H, pyran),7.10-8.60 (m,8H,arom.)	56.95 (56.81)	3.04 (3.15)	15.10 (15.21)	6.92 (6.79)	7.65 (7.53)
8d	70	120-122	$C_{20}H_{13}N_4O_2SCl$	3391(NH),3053 (CH arom.),2919 (CH aliph.)	(CF_3COOD):3.70-3.95 (m,4H,$2CH_2$),5.00(s,1H, pyran),6.80-8.40(m,7H, arom.)	58.74 (58.58)	3.20 (3.12)	13.70 (13.83)	7.85 (7.71)	8.68 (8.53)
8e	64	253-255	$C_{20}H_{13}N_4OS_2Cl$	3400(NH),3053 (CH arom.)	(CF_3COOD):3.70-3.95 (m,4H,$2CH_2$),5.00(s,1H, pyran),6.80-8.40(m,7H, arom.)	56.51 (56.66)	3.08 (3.19)	13.19 (13.05)	7.55 (7.42)	8.35 (8.23)
9a	64	170-172	$C_{19}H_{10}N_4OCl_2$	3000(CH arom.), m/z 381	($CDCl_3$):5.05(s,1H, pyran),7.00-8.60(m,9H, arom.)	59.84 (59.73)	2.64 (2.15)	14.70 (14.81)	- -	18.62 (18.72)
9b	69	114-116	$C_{20}H_{12}N_4O_2Cl_2$	2945(CH arom.), m/z 411	($CDCl_3$):5.00(s,1H, pyran),7.00-8.50(m,8H, arom.)	58.40 (58.27)	2.94 (2.85)1	13.62 (13.49)	- -	17.25 (17.28)
9c	58	185-187	$C_{19}H_9N_5O_3Cl_2$	3000(CH arom.)	($CDCl_3$):5.10(s,1H, pyran),7.10-8.60(m,8H, arom.)	53.53 (53.67)	2.13 (2.24)	16.43 (16.56)	- -	16.66 (16.52)
9d	55	250-252	$C_{17}H_8N_4O_2Cl_2$	3083(CH arom.), m/z 371	($CDCl_3$):5.00(s,1H, pyran),6.80-8.40(m,7H, arom.)	54.99 (54.84)	2.17 (2.06)	15.09 (15.24)	- -	19.12 (19.26)
9e	57	200-202	$C_{17}H_8N_4OSCl_2$	3000(CH arom.)	($CDCl_3$):5.00(s,1H, pyran),6.80-8.30(m,7H, arom.)	52.71 (52.84)	2.08 (2.19)	14.47 (14.34)	8.29 (8.15)	18.33 (18.21)
10a	80	197-199	$C_{19}H_{13}N_6OCl$	3324-3180 (NH2), 3477 (NH); 3048 (CH arom.)	($CDCl_3$):4.30(s,2H, NH_2),5.00(s,1H,pyran), 7.00-8.60(m,9H,arom.)	60.55 (60.69)	3.48 (3.57)	22.31 (22.45)	- -	9.42 (9.56)
10b	77	193-195	$C_{20}H_{15}N_6O_2Cl$	3350-3201 (NH2)	($CDCl_3$):2.20(s,3H, CH_3),4.30(s,2H,NH_2), 4.90(s,1H,pyran),7.00-8.50(m,8H,arom.), 8.90(s,1H,NH)	59.04 (59.17)	3.72 (3.81)	20.66 (2054)	- -	8.73 (8.60)
10c	66	146-148	$C_{19}H_{12}N_7O_3Cl$	3339-3206 (NH2)	($CDCl_3$):4.40(s,2H, NH_2),5.00(s,1H,pyran),7 .10-8.60(m,8H,arom.), 8.95(s,1H,NH)	54.09 (54.24)	2.87 (2.94)	23.25 (23.37)	- -	8.42 (8.51)
10d	75	154-157	$C_{17}H_{11}N_6O_2Cl$	3324-3201 (NH2)	($CDCl_3$):4.30(s,2H,NH_2) 5.00(s,1H,pyran),6.75-8.40(m,7H,arom.), 8.80(s,1H,NH)	55.66 (55.54)	3.02 (2.94)	22.92 (22.79)	- -	9.68 (9.56)
10e	68	260-262	$C_{17}H_{11}N_6OSCl$	3330-3230 (NH2)	($CDCl_3$):4.30(s,2H, NH_2),5.00(s,1H,pyran), 6.70-8.40(m,7H,arom.), 8.80(s,1H,NH)	51.32 (51.47)	2.79 (2.88)	21.13 (21.28)	8.07 (8.16)	8.92 (8.79)
11a	74	178-180	$C_{20}H_{11}N_6OCl$		($CDCl_3$):5.00(s,1H, pyran),6.60(s,1H, triazol),7.10-8.60(m,9H, arom.)	62.09 (62.21)	2.87 (2.94)	21.73 (21.62)	- -	9.18 (9.25)

Table-1 (continued): Physical data of the newly synthesized compounds 2a-e-13a-e

11b	68	250-252	$C_{21}H_{13}N_6O_2Cl$		($CDCl_3$):2.25(s,3H, CH_3),5.00(s,1H,pyran), 6.00(s,1H,triazol),7.00-8.40(m,8H,arom.)	60.50 (60.35)	3.14 (3.08)	20.17 (20.29)	- -	8.52 (8.44)
11c	61	>300	$C_{20}H_{10}N_7O_3Cl$		($CDCl_3$):5.00(s,1H, pyran),6.60(s,1H, triazol),7.10-8.50(m,8H, arom.)	55.62 (55.49)	2.33 (2.40)	22.71 (22.60)	- -	8.22 (8.35)
11d	67	>300	$C_{18}H_9N_6O_2Cl$		($CDCl_3$):4.90(s,1H,pyra n),6.50(s,1H,triazol), 6.80-8.20(m,7H,arom.)	57.37 (57.48)	2.41 (2.52)	22.31 (22.20)	- -	9.42 (9.31)
11e	59	>300	$C_{18}H_9N_6OSCl$		($CDCl_3$):4.90(s,1H, pyran),6.50(s,1H, triazol),6.80-8.20(m,7H, arom.)	55.02 (55.15)	2.31 (2.24)	21.39 (21.26)	8.17 (8.20)	9.04 (9.17)
12a	64	166-168	$C_{20}H_{11}N_6OSCl$	3334 (NH),1190 (CS)	(CF_3COOD):5.00(s,1H, pyran),7.00-8.50(m,9H, arom.)	57.33 (57.48)	2.65 (2.74)	20.07 (20.19)	7.66 (7.52)	8.47 (8.34)
12b	58	193-195	$C_{21}H_{13}N_6O_2SCl$	3339-3206 (NH)	(CF_3COOD):2.20(s,3H, CH_3),5.00(s,1H,pyran), 7.10-8.40(m,8H,arom.)	56.18 (56.06)	2.92 (2.84)	18.72 (18.62)	7.15 (7.26)	7.91 (7.82)
12c	56	99-101	$C_{20}H_{10}N_7O_3SCl$	3350 (NH)	(CF_3COOD):5.00(s,1H, pyran),7.10-8.60(m,8H, arom.)	51.77 (51.63)	2.17 (2.25)	21.14 (20.28)	6.92 (6.81)	7.65 (7.52)
12d	60	>300	$C_{18}H_9N_6O_2SCl$	3206 (NH)	(CF_3COOD):5.00(s,1H, pyran),6.80-8.30(m,7H, arom.)	52.87 (52.71)	2.22 (2.31)	20.56 (20.41)	7.85 (7.70)	8.68 (8.52)
12e	54	180-182	$C_{18}H_9N_6OS_2Cl$	3355(NH), m/z 425	(CF_3COOD):5.00(s,1H, pyran),6.80-8.30(m,7H, arom.)	50.87 (50.92)	2.14 (2.21)	19.78 (19.66)	15.11 (15.23)	8.35 (8.23)
13a	61	161-163	$C_{19}H_{10}N_7OCl$	2182 (N_3)	($CDCl_3$):4.95(s,1H, pyran),7.10-8.50(m,9H, arom.)	58.84 (58.71)	2.60 (2.50)	25.29 (25.15)	- -	9.15 (9.26)
13b	59	183-185	$C_{20}H_{12}N_7O_2Cl$	2121 (N_3)	($CDCl_3$):2.20(s,3H, CH_3),5.00(s,1H,pyran), 7.00-8.30(m,8H,arom.)	57.48 (57.33)	2.90 (2.83)	23.47 (23.32)	- -	8.50 (8.41)
13c	55	133-135	$C_{19}H_9N_7O_2Cl$	2182 (N_3)	($CDCl_3$):5.00(s,1H, pyran),7.10-8.60(m,8H, arom.)	54.48 (54.85)	2.17 (2.17)	25.89 (25.77)	- -	8.48 (8.17)
13d	63	>300	$C_{17}H_8N_7O_2Cl$	2126 (N_3)	($CDCl_3$):5.00(s,1H, pyran),6.80-8.20(m,7H, arom.)	54.04 (54.19)	2.14 (2.05)	25.96 (25.80)	- -	9.40 (9.27)
13e	57	>300	$C_{17}H_8N_7OSCl$	2126 (N_3)	($CDCl_3$):5.00(s,1H, pyran),6.80-8.20(m,7H, arom.)	51.83 (51.66)	2.03 (2.16)	24.90 (24.74)	8.15 (8.29)	9.01 (9.16)

Antifungal Activity

The newly synthesized compounds were screened for their antifungal activity against three species of fungi, namely, Aspergillus flavus, Aspergillus niger and Penicillium chrysegenum using the disk diffusion method(22,23) and results of the biological testing are given in Table 2. The data showed that most of the newly synthesized compounds exhibited remarkable effects.

Table-2: Antifungal screening of compounds (2a-e – 13a-e) (inhibition zones mm)

Comp. No.	Aspergillus flaves	Aspergillus niger	Penicillium Chrysogenum
2a	25	32	23
2b	30	24	26
2c	29	27	22
2d	14	17	15
2e	12	15	13
3a	11	14	14
3b	13	16	14
3c	6	4	10
3d	9	6	8
3e	26	31	22
4a	29	25	27
4b	31	29	24
4c	15	18	16
4d	14	16	13
4e	28	24	33
5a	17	15	13
5b	25	21	26
5c	8	6	9
5d	9	8	11
5e	13	16	18
6a	17	12	14
6b	9	7	11
6c	6	8	4
6d	3	5	6
6e	33	29	26
7a	27	24	31
7b	19	19	17
7c	17	15	16
7d	18	15	13
7e	40	36	31
8a	36	28	37
8b	19	13	15
8c	8	7	6
8d	6	4	8
8e	35	31	26
9a	29	23	21
9b	31	28	25
9c	15	17	20
9d	12	13	11
9e	14	11	14
10a	13	16	18
10b	34	28	31
10c	11	14	12
10d	13	12	10
10e	8	5	6
11a	8	8	6
11b	7	9	10
11c	5	6	5
11d	9	4	7
11e	38	40	33

12a	**31**	**36**	**26**
12b	**34**	**27**	**29**
12c	**9**	**10**	**11**
12d	**6**	**8**	**4**
12e	**30**	**27**	**22**
13a	**25**	**32**	**26**
13b	**29**	**24**	**24**
13c	**15**	**16**	**14**
13d	**18**	**13**	**16**
13e			
Tetracyclin	**9**	**10**	**12**

References

1. M.P. Georgiadis, E.A. Cauladouros and A.K. Delitheos, *J. Pharm. Sci.* **81**, 1126 (1992).
2. J. Zamocka, E. Misikova and J. Durinda, *Cesk. Pharm.* **41**,170 (1992); *Chem. Abstr.* **116** 106031 q (1992).
3. T. Ohira and M. Yatagai, *J. Jpm. Wood Res. Soc.* **39**, 237 (1993); *Chem. Abstr.* **119**, 19585 d (1993).
4. S.J. Mohr, M.A. Chirigos, F.S. Fuhrman and J.W. Pryor, *Cancer Res.* **35**, 3750 (1975).
5. F.Eiden and F. Denk, *Arch Pharm Weinnheim Ger.* **324**, 353 (1991).
6. V.K. Tandon, M. Vaish, S. Jain, D.S. Bhakuni and R.C. Srimal, *Indian J. Pharm Sci.* **53**, 22 (1991).
7. V.J. Kam, *Indian J. Chem.* **28B**, 159 (1989).
8. A. Richardson and F.J. McCarry, *J. Med. Chem.* **15**, 1203 (1972).
9. P.K. Nalthani, V.K. Srivastava, T.K. Gupta and K. Shanker, *J. Indian Chem. Soc.* 68, 422 (1991).
10. V.J. Ram, *J. Prakt Chem.* **331**, 893 (1989).
11. A.A.A. Hafez, *J. Chem. Technol. Biotechnol*, **55**, 95 (1992).
12. S. Mehrota, J.P. Barthcal, B.R. Pandey, K.P. Bhargava and S.S. Parmar, *J. Heterocyclic Chem.* **17**, 1213 (1980).
13. A. Kumar, K.K. Saxena, V.K. Srivastava, S. Lata and R.S. Saxena, *J. Indian Chem. Soc.* **68**, 138 (1991).
14. S., Yu. O. Cha, K. Lee, H. Shin, J. Seo, N. Kim, E. Jung, S. Kim and H. Seo (Korea Research Institute of Chemical Technology, S. Korea) KR 132,014 (Cl. CO7D401/14)(17 Apr. 1998, Appl. 9 402/681, 16 Feb. 1994); *Chem. Abstr.* **133**(17), 238001 r (2000).
15. T. Saro, T. Taguchi, H. Nakano, T. Inoue and N. Kawasaki, (K.K. Fuji Vakuhin, Japan) Jpn. Kokai Tokkyo koho Jp 2000 256.354 (Cl CO7D403/04)(19 Sep. 2000. Appl. 1999/55,531,3 March 1999. 18 pp.), *Chem. Abstr.* **133**(17), 238002 s (2000).
16. S. Iehr, K. Kather, H. Riebel, K. Voigr, M. Drewes and R. Pantzen, (A.G. Bayer, Germany) Ger. Often DE 19,927,611 (Cl CO/D251/8)(21 Dec. 2000, Appl.19, 927, 611, 17 June 1999, 40pp.); *Chem. Abstr.* **134**(5), 56694 g (2001).
17. A.A. Abdel Hafez and I.M.A. Awad, *Dyes Pigm*, **20**, 197 (1992).
18. Z.H. Khalil, A.A. Abdel Hafez, A.A. Geies and A.M. Kamal El-Dean, *Bull Chem. Soc. Jpn.* 64, 668 (1991).
19. A.A. Abdel Hafez, A.M. Kamal El-Dean, A.A.Hasan, H.S. El-Kashef, S. Rault and M. Robba, *J. Heterocycl Chem.* **33**, 431 (1996).
20. A.A. Abdel Hafez, *Collect Czech Chem. Commun.* **58**, 2222 (1993).
21. A.A. Abdel Hafez and I. M. A. Awad, *Phosphorus sulfur, Silicon* **71**, 453 (1992).
22. L.P. Carrod and P.D. Grady, *Antibiotic and Chemotherapy*, 3rd ed., Churchill Livingstone Edinburgh p. 477 (1927).
23. A. Cremer, *Antibiotic Sensitivity and Assay Tests*, 4th ed. Butterworth, London, p. 521 (1980).

Received on March 18, 2005