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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME PYRIDINE SUBSTITUTED HETEROCYCLIC COMPOUNDS

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Some pyridine substituted heterocyclic compounds and their derivatives such as, imidazolone, quinazolone, benzimidazole, phthalimide, thioxopyrimidindione, pyrazole, 1,2,4-triazinone and thiazolidinone (IV-XXVII) have been prepared and screened for their antibacterial and antifungal activities, which gave encouraging results. The structures of the products have been verified by elemental analysis and spectral data (IR, UV, ^{1}H NMR and mass).

Key words: Heterocyclic, Substituted pyridines, Biological activity.

Introduction

Substituted pyridines have emerged as versatile reagents recently and their biological activities have received a considerable attention [1-6]. In continuation of our study [7], the synthesis and biological activity of pyridine substituted heterocyclic compounds is reported. The sequence of these reactions is depicted in Schemes I and II.

Experimental

All the reported melting points were recorded. UV spectra were recorded in DMF on a Perkin-Elmer, Lambda 4B Controller Accessory Interface, uv-vis Spectrophotometer (λ_{max} in nm). IR spectra were recorded in KBr on a Perkin-Elmer, 1430 Ratio Recording Spectrophotometer (υ_{max} in cm^{-1}). ^{1}H NMR spectra were recorded on Bruker 200 MHz/ 52 MM spectrometer using DMSO-d_6 as a solvent and TMS as an internal reference (chemical shifts in δ, ppm). Mass spectra were recorded using a Hewlett-Packard model: MS 5988 Spectrometer (70 eV).

Reaction of 2-amino-6-methylpyridine (I) and/or 4-aminopyridine (II) with 4-(p-nitrobenzylidene)-2-phenyl-2-oxazol-5-one (III): Formation of IV and/or XVII. An equimolar mixture of compounds I and/or II with III in gl. acetic acid (10 ml) was refluxed for 10 hrs, cooled, poured into crushed ice and filtered off. The solid thus obtained was recrystallized to give IV and/or XVII (Table 1). IR (IV): 3109 (aromatic CH), 1696 (C=O), 1649 (C=C), 1599, 1582 (C=N), 1518, 1325 (asy. and sy. NO_2), 1344 (N-C-N), 1226 (C-N), 780 and 765 (phenyl group) and UV: 410, 376.4 and 274.6 (due to conjugation of n-π^*, π-π^* and n-σ^*, respectively). IR (XVII): 3071 (aromatic CH), 1761 (C=O), 1654 (C=C), 1600 (C=N), 1582 (C=N of pyridine), 1519, 1326 (asy. and sy. NO_2), 1345 (N-C-N), 1225 (C-N), 824, 780, 765 (phenyl group) and 702 (C-Cl); UV: 373 and 274.

Synthesis of 2,3-disubstituted-4-(3H)-quinazolinones (VI) and/or (XVIII). A mixture of I and/or II with V in dry pyridine (10 ml) was refluxed for 10 hr, cooled, poured onto ice-HCl and filtered off. The resultant solid was recrystallized to give VI and/or XVIII (Table 1). IR (VI): 2955-2841 (aliphatic CH), 1755 (C=O), 1658-1646 (C=N endo), 1504, 1450 (def. CH), 816, 786, 764, 747 (phenyl group) and 690 (C-Cl). IR (XVIII): 3079 (aromatic CH), 1730 (C=O), 1606 (C=C pyridine ring), 1583, 1574 (C=N), 818, 760, 748 (phenyl group and 675 (C-Cl). M/z (Int. %) (XVIII): 335 (0.4), 255 (19.9), 135 (100), 118 (0.4), 90 (1.9), 78 (2.5) and 76 (1.8).

Reaction of I and/or II with 2-methylbenzoxazole (VII): Formation of VIII and/or XIX. An equimolar mixture of I and/or II with 2-methylbenzoxazole (VII) in dry pyridine (10 ml) was refluxed for 10 hr, cooled, poured onto ice-HCl and filtered off. The solid obtained was recrystallized to give VIII and/or XIX (Table 1). IR (VIII): 3087 (aromatic CH), 2975-2877 (aliphatic CH), 1658, 1614 (C=C, C=N of pyridine), 1595 (C=N), 1451 (def. CH), 1331 (N-C-N), 1202 (C-N), 812 and 767 (phenyl group). IR (XIX): 2876 (aliphatic CH), 1596 (C=N), 1503, 1452 (def. CH), 1324 (N-C-N), 1203 (C-N), 767 and 721 (phenyl group).

Synthesis of 1-(6'-methylpyridin-2'-yl)-2-methylbenzimid azole (X) and 1-(pyridin-4'-yl)-2-methylbenzimidazole (XX). Compound VIII and/or XIX was stirred with conc. H_2SO_4 for 2 hr, and neutralized with aq. NaOH. The reaction mixture was extracted with ether and the solid obtained was recrystallized to give X and/or XX (Table 1).

Condensation of I with phthalic anhydride: Formation of IX. A mixture of I (0.01 mole) and phthalic anhydride (0.01 mole) in gl. acetic acid (10 ml) was heated under reflux for 4 hr, cooled, poured onto crushed ice and filtered off. The separated solid was washed with cold water and recrystallized to give IX (Table 1). IR: 3078 (NH & aromatic CH), 2807 (aliphatic CH), 1692, 1678 (two C=O), 1642 (C=C), 1554 (C=N), 1468, 1432 (def. CH), 1353 (N-C-N), 1227 (C-N), 792 and 722 (phenyl group).

Cyclization of IX: Formation of N-(6'-methylpyridine-2'-yl)-phthalimide (XI). Compound IX was refluxed with aq. NaOH (10%, 20 ml) for 2 hr and acidified with HCl. The solid obtained was filtered off to give XI (Table 1). IR: 2659 (aliphatic CH), 1745 and 1708 (two C=O), 1647, 1588 (C=C, C=N), 1490, 1465 (def. CH), 1387, 1322 (N-C-N), 1205 (C-N), 984, 911 and 897 (phenyl group).

Synthesis of N-(pyridin-4'-yl)phthalimide (XXI). A mixture of II (0.01 mole) and phthalic anhydride (0.01 mole) in gl. acetic acid (10 ml) was heated under reflux for 4 hr, cooled, poured onto crushed ice and filtered off. The separated solid was washed with cold water and recrystallized to give XXI (Table 1). IR; 3051 (aromatic CH), 1750, 1712 (two C=O), 1611, 1589 (C=C) andC=N), 1228 (C-N), 791 and 737 (phenyl group).

Reaction of I with allyl isothiocyanate and/or II with phenylisocyanate: Formation of XII and/or XXII. An equimolar mixture of I with allyl isothiocyanate and/or II with phenyl isocyanate in DMF (10ml) was refluxed for 1 hr, cooled and poured onto crushed ice. The solid obtained was triturated from methanol to give XII and/or XXII (Table 1). IR (XXII): 3196, 3134 (two NH), 3036 (aromatic CH), 1647 (C=O), 1594 (C=N), 789 and 753 (phenyl group).

TABLE 1. CHARACTERIZATION DATA OF VARIOUS COMPOUNDS PREPARED, IV-XXVII.

Compd.	Cryst. solvent	M.P °C	Yield (%)	Mol. Formula*
IV	AcOH	237-238	60	$C_{22}H_{16}N_4O_3$
VI	EtOH	219-220	50	$C_{20}H_{14}N_3ClO$
VIII	EtOH	211-212	70	$C_{14}H_{15}N_3O$
IX	EtOh	175-176	60	$C_{14}H_{12}N_2O_3$
X	Ethyl benzene	>270	50	$C_{14}H_{13}N_3$
XI	AcOH	165-166	55	$C_{14}H_{10}N_2O_2$
XII	Dil. DMF	166-167	50	$C_{10}H_{13}N_3S$
XIII	Dil. MeOH	166-167	40	$C_{13}H_{13}N_3SO_2$
XIV	Pet. ether	90-91	60	$C_{10}H_{12}N_2O_2$
XV	Dil. AcOH	>290	50	$C_{16}H_{16}N_4$
XVI	Dil. EtOH	192-193	50	$C_{16}H_{14}N_6O_4$
XVII	EtOH	240-241	40	$C_{21}H_{14}N_4O_3$
XVIII	EtOH	235-236	45	$C_{19}H_{12}N_3ClO$
XIX	EtOH	208-209	70	$C_{13}H_{13}N_3O$
XX	Benzene	>275	50	$C_{13}H_{11}N_3$
XXI	EtOH	194-195	65	$C_{13}H_8N_2O_2$
XXII	Dil. EtOH	236-237	50	$C_{12}H_{11}N_3O$
XXIII	EtOH	141-142	40	$C_{15}H_{11}N_3O_3$
XXIVa	-	Oil	-	$C_9H_{12}N_2O_2$
XXIVb	MeOH	>275	50	$C_7H_{10}N_4O_2$
XXVa	Dil. AcOH	>290	40	$C_9H_{10}N_4O$
XXVb	EtOH	240-241	40	$C_{14}H_{11}N_5O_3$
XXVI	EtOH	>280	60	$C_7H_6N_2O_2$
XXVII	MeOH	263-264	55	$C_9H_8N_2SO_3$

*All compounds were also analyzed for C, H, N, Cl, S and the analytical results were within ± 0.4 - 0.5%.

Reaction of XII and/or XXII with malonic acid: Formation of XIII and/or XXIII. Compound XII and/or XXII (0.01 mole) and malonic acid (0.01 mole) in acetyl chloride (7 ml) was refluxed for 6 hr on steam-bath. It was then poured onto crushed ice. The resultant solid was recrystallized to give XIII and/or XXIII (Table 1). IR (XIII): 3052 (aromatic CH), 2988 (aliphatic CH), 1730, 1680 (two C=O), 1648 (C=C), 1609, 1552 (C=C, C=N of pyridine), 1450 (def. CH) 1379 (N-C-N) and 1200 (C-S). ^{1}H NMR (XIII): 2.4 (*s*, 2H, CH_3), 4.3 (*s*, ^{1}H,=CH of pyrimidine ring), 5.2 (*m*, 2H, =CH), 6.0 (*m*, ^{1}H=CH) 7.0 (*m*, 2H, CH_2 of allyl moiety), 7.6 (*m*, 3H, pyridine protons), 10.6 (*s*, ^{1}H, OH) and 12.0 (*s*, 1H, OH of 4, 6-dihydroxypyrimidine). M/z (Int.%) (XIII): 275 (0.9), 240 (0.9), 191 (100), 126 (2.8), 98 (2.7), 83 (1.8) and 71 (3.9). IR (XXIII): 3675-3364 (OH), 3071 (aromatic CH), 1734, 1713 (two C=O), 1633 (C=C), 1600, 1552 (two C=N), 1452, 1416 (def. CH), 1233 (N-CO-N), 928, 909, 877 and 844 (phenyl group).

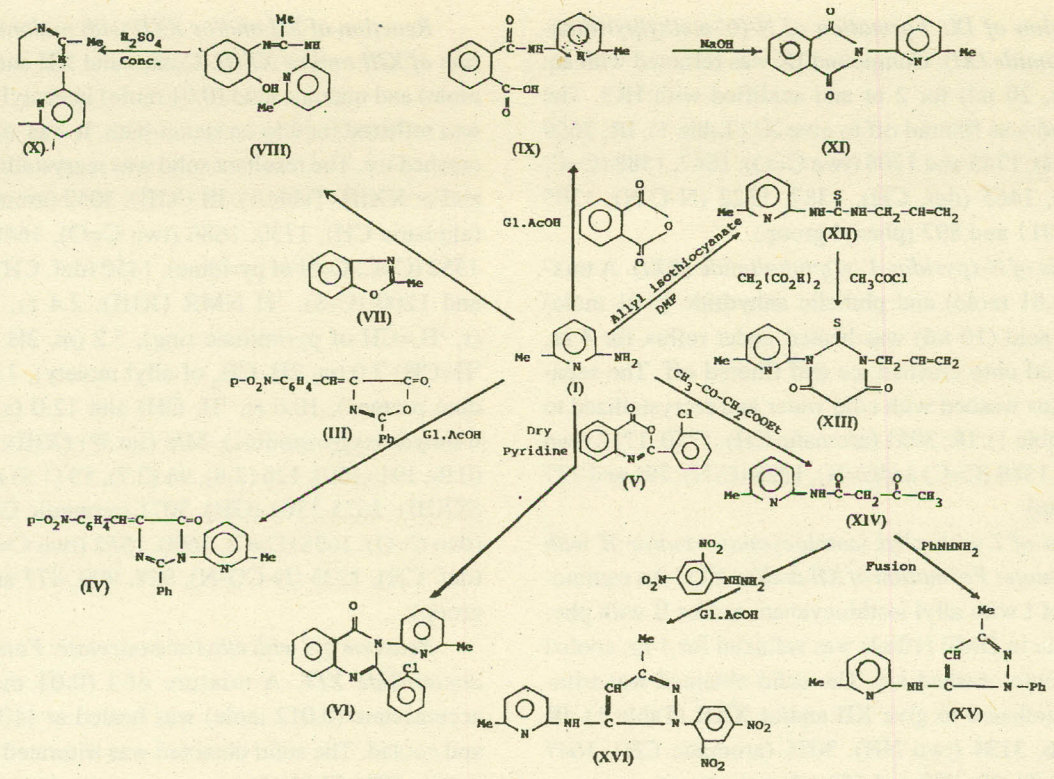
Reaction of I with ethyl acetoacetate: Formation of acetyl acetanilide XIV. A mixture of I (0.01 mole) and ethyl acetoacetate (0.012 mole) was heated at 110°C for 15 min. and cooled. The solid obtained was triturated from methanol to give XIV (Table 1).

Reaction of XIV with phenylhydrazine: Formation of XV. Compound XIV (0.01 mole) was fused with phenylhydrazine (0.01 mole) for 15 min. The resultant solid was triturated from methanol to give XV (Table 1). IR: 3070 (NH), 2856 (aliphatic CH), 1601 (C=C), 1566 (C=N), 1493, 1455 (def. CH), 722 and 747 (phenyl group). M/z (Int.%): 264 (0.4), 77 (100), 187 (0.5), 94 (3.3), 93 (7.8), 79 (2.4), 64 (6.6) and 51 (24.7).

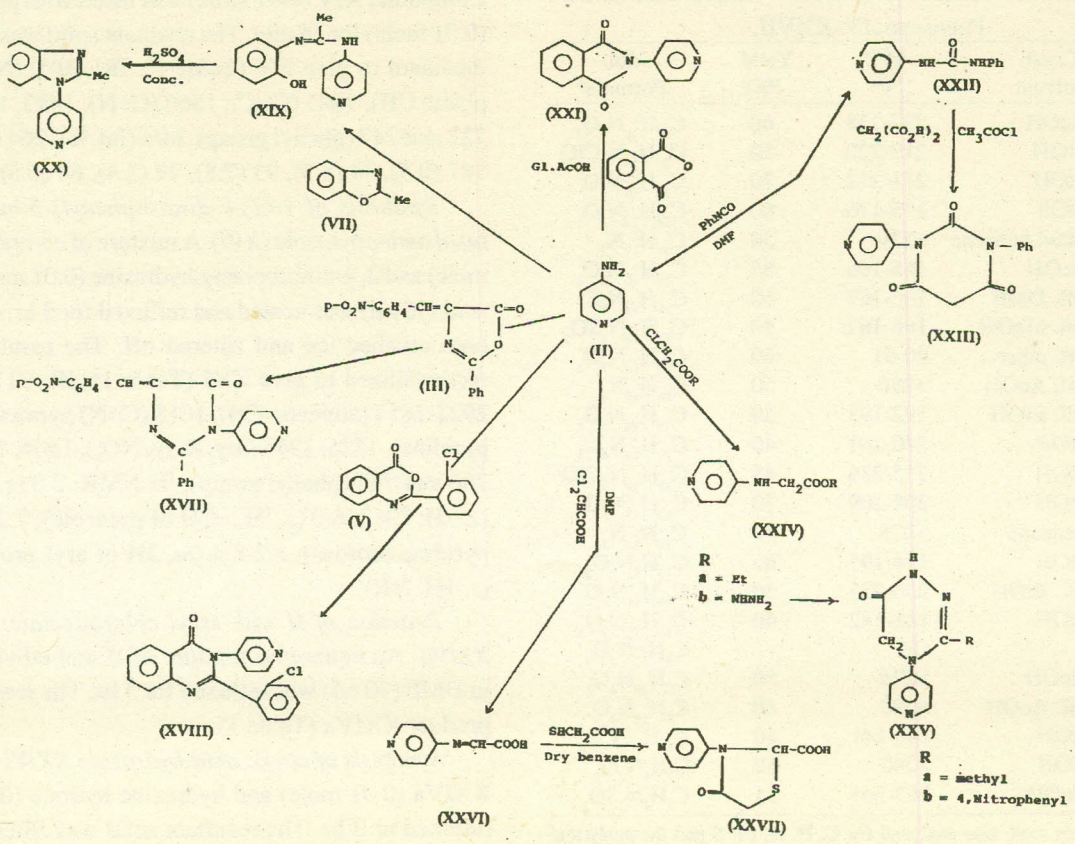
Synthesis of 1-(2',4'-dinitrophenyl)-3-methyl-5-substituted aminopyrazole (XVI). A mixture of compound XIV (0.01 mole) and 2, 4-dinitrophenylhydrazine (0.01 mole) in gl. acetic acid (10 ml) was heated and refluxed for 3 hr, cooled, poured onto crushed ice and filtered off. The resultant solid was recrystallized to give XVI (Table 1). IR: 3113-3087 (NH), 2922-2853 (aliphatic CH), 1618 (C=N) pyrazole), 1588 (C=N pyridine), 1526, 1345 (asy. & sy. NO_2), 1504, 1418 (def. CH), 786 and 743 (phenyl group). ^{1}H NMR: 2.0 (*s*, 3H, CH_3), 3.5 (*s*, 3H, CH_3), 6.0 (*s*, ^{1}H, =CH of pyrazole), 7.2-7.4 (*m*, 3H of pyridine protons), 8.2-8.4 (*m*, 3H of aryl protons) and 10.4 (*s*, 1H, NH).

Reaction of II with ethyl chloroacetate: Formation of XXIVa. An equimolar mixture of II and ethyl chloroacetate in DMF (10 ml) was refluxed for 3 hr. The reaction gave oily product XXIVa (Table 1).

Synthesis of acetic acid hydrazide XXIVb. A mixture of XXIVa (0.01 mole) and hydrazine hydrate (0.02 mole) was refluxed or 3 hr. The resultant solid was filtered off and recrystallized to give XXIVb (Table 1).



Scheme I



Scheme II

Synthesis of 3-methyl-4-(pyridine-4'-yl)-5-dihydro-1,2,4-triazin-6-(1H)one (XXVa). Compound XXIVb (0.01 mole) and fused sodium acetate (5 g) in gl. acetic acid (10 ml), were heated under reflux for 4 hr, cooled and poured onto crushed ice. The separated solid was filtered off and recrystallized to give XXVa (Table 1). IR: 3678 (OH), 3268-3059 (NH), 2944 (aliphatic CH), 1678 (C=O), 1658 (C=C), 1609 (C=N), 1519, 1445 (def. CH), 1369 (N-C-N) and 1228 (C-N).

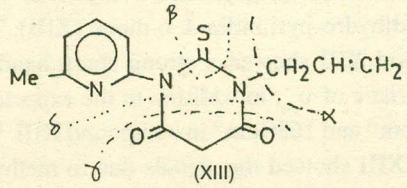
Synthesis of 3-(p-nitrophenyl)-4-(pyridin-4'-yl)-5-dihydro-1,2,4-triazin-6-(1H)-one (XXVb). Compound XXIVb (0.01 mole) and *p*-nitrobenzoyl chloride (0.01 mole) in dry pyridine (10 ml) were heated and refluxed for 15 min, and then in abs. ethanol (20 ml) for 4 hr, cooled and poured onto crushed ice. The solid obtained was filtered off and recrystallized to give XXVb (Table 1). IR: 3749 (OH), 3121 (NH), 3070 (aromatic CH), 2993, 2857 (aliphatic CH), 1692 (C=O), 1608 (C=N), 1538, 1352 (asy. & sy. NO_2), 1494, 1427 (def. CH), 1311 (N-C-N), 822, 790 and 717 (aryl and pyridine groups). ^{1}H NMR: 2.5 (*s*, 2H, CH_2), 7.9-8.1 (*m*, 4H, of pyridine) and 8.2-8.5 (*m*, 5H, of aryl and NH protons).

Reaction of II with dichloroacetic acid: Formation of XXVI. A mixture of II (0.01 mole) and 1, 1'-dichloroacetic acid (0.01 mole) in DMF (10 ml) was refluxed for 3 hr. The resultant solid was filtered off and recrystallized to give XXVI (Table 1). IR: 3433 (OH), 3040 (pyridine ring), 2797 (aliphatic CH), 1781 (C=O), 1643 (exo C=N), 1604, 1572 (C=C, C=N), 1472 and 1417 (def. CH). UV: λ_{max} at 275.8 (due to conjugation of n -π*, π-π*).

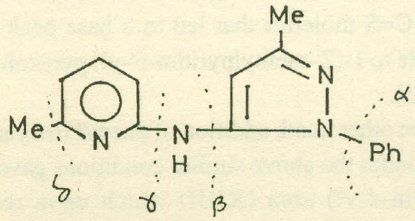
Reaction of XXVI with mercaptoacetic acid: Formation of XXVII. A mixture of XXVI (0.01 mole) and thioglycolic acid (0.02 mole) in dry benzene (10 ml) was refluxed for 8 hr. The solid obtained was filtered off and recrystallized to give XXVII (Table 1). IR: 3445 (OH), 3026 (aromatic CH), 2915, 2847 (aliphatic CH), 1776, 1642 (two C=O), 1605, 1573 (C=C, C=N), 1473, 1416 (def. CH) and 1162 (C-S); UV: 275.8. ^{1}H NMR: 5.0 (*s*, 1H, CH-COO-), 6.4 (*s*, 1H, =CH cyclic), 6.8-7.2 (*m*, 4H, of pyridine), 9.5 and 14.0 (each *s*, OH of thiazole and COOH moiety).

Results and Discussion

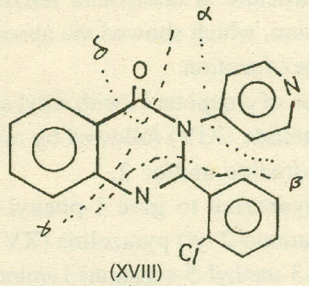
Condensation of 2-amino-6-methylpyridine (I) and/or 4-aminopyridine (II) with 4-(*p*-nitrobenzylidene)-2-phenyl-2-oxazol-5-one (III) in the presene of gl. acetic acid [8] gave 1-(6'-methylpyridine-2'-yl)-2-phenyl-4-(*p*-nitrobenzylidene) imidazol-5-one (IV) and/or 4-(pyridin-4'-yl)-2-phenyl-4-(*p*-nitrobenzylidine) imidazol-5-one (XVII). While the condensation of I and/or II with 2-(2'-chlorophenyl)-4H-3, 1 benzonazin-4-one (V) in dry pyridine [8] led to the formation of 2 (2'-chlorophenyl)-3-(2'-methylpyridin-6'-yl) quinazolin-4-one (VI) and 2-(2'-chlorophenyl)-3-(pyridin-4'-yl) quinazolin-4-one (XVIII), respectively. The structures of compounds IV, VI, XVII and XVIII were characterized by spectral data and elemental analyses. From inspection of their IR spectra, it is evident that both NH_2 and NH bands were disappeared. Mass spectrum of XVIII revealed the molecular ion peak at m/z 335 (M+1), which upon fragmentation process gave the base peak at m/z 135 (Scheme III).



(XIII)
m/z 275
240 (0.9), 191 (100), 71 (3.9), 126 (2.8), 98 (2.7), 83 (1.8)



(XV)
m/z 264
77 (100), 187 (0.5), 94 (3.3), 93 (7.8), 79 (2.4), 64 (6.6), 51 (24.7)



(XVIII)
m/z 335
255 (19.9), 135 (100), 118 (0.4), 90 (1.9), 78 (2.5), 76 (1.8)

Scheme III. Mass fragmentation of compounds XIII, XV and XVIII.

Compounds I and/or II on treatment with 2-methylbenzoxazole (VII) in dry pyridine [10] gave 2-iminophenol derivatives VIII and/or XIX which on stirring with conc. H_2SO_4 afforded 1-6'-methylpyridin-2'-yl)-2-methyl-benzimiazole (X) and/or 1-(pyridin-4'-yl)-2-methylbenzimidazole (XX). The IR spectra of VIII and XIX showed significant bands for the OH and NH groups, which upon their condensation give compounds X and XX.

Reaction of compound I with phathalic anhydride in the presence of gl. acetic acid, yielded *o*-benzanilidobenzoic acid (IX) which underwent basic cyclization by boiling with aq. NaOH and afforded *N*-(6'-methylpyridin-2'-yl) phthalimide (XI), while in the case of compound II on refluxing with phathalic anhydride in gl. acetic acid, *N*-(pyridin-4'-yl) phthalimide (XXI) was isolated. Structures of XI and XXI

were substantiated from (i) analytical data and (ii) their IR spectra which showed the characteristic absorptions of substituted phthalimide.

Addition of allyl isothiocyanate to compound I in DMF afforded [11] N^1-allyl-N^2-(6-methylpyridin-2-yl) thiourea (XII) which on treatment with malonic acid in the presence of acetyl chloride [11] yielded 1-allyl-3-(6'-methylpyridin-2'-yl)-5-dihydro-pyrimidin-4, 6-dione (XIII). The IR spectra of XII and XIII showed a strong sharp band at 1200 cm^{-1} characteristic of υ_{c-s}, in addition to the expected C=O bands at 1730 cm^{-1} and 1680 cm^{-1} in compound XIII. ^{1}H NMR spectrum of XIII showed the signals due to methyl, methylene, allyl and pyridine protons, while its mass fragmentation showed the molecular ion peak at m/z 275, via the loss of allyl and C=S moieties that led to a base peak at m/z 191, attributable to 1-(2'-methylpyridin-6'-yl) pyrazolin-3, 5-dione (Scheme 3).

On the other hand, addition of phenyl isocyanate to compound II under the above similar conditions gave N^1-phenyl-N^2-(pyridin-4-yl) urea (XXII) which upon reaction with malonic acid in the presence of acetyl chloride gave 1-phenyl-3-(pyridin-4'-yl)-5-dihydropyrimidin-2,4,6-trione (XXIII). The structure of compound XXIII was confirmed by its IR spectrum, which showed the absorption bands due to trione complex function.

The reaction of compound I with ethyl acetoacetate gave the acetyl acetanilide (XIV) followed by cyclocondensation with phenylhydrazine and/or 2, 4-dinitrophenylhydrazine to give 1-phenyl-3-methyl-5-(6'-methylpyridin-amino-2'-yl) pyrazoline (XV) and/or 1-(2'-4'-dinitro-phenyl)-3-methyl-5-substituted aminopyrazole (XVI). The structures of compounds XV and XVI were deduced from their elemental analyses and spectral data. Their IR spectra did not show any absorption bands for carbonyl groups. Mass spectrum of XV gave supported evidence for the postulated structure, which showed the molecular ion peak at m/z 264, which on further fragmentations furnished the phenyl ion as a base peak (Scheme 3). ^{1}H NMR spectrum of XVI showed the presence of signals which are attributed to methyl, aryl and C-H of pyrazole protons.

Treatment of compound II with ethyl chloroacetate in DMF [12] gave α-substituted amino ethyl acetate XXIVa, which on treatment with hydrazine hydrate afforded α–substituted aminoacetic acid hydrazide XXIVb. Refluxing of XXIVb with gl. acetic acid-fused sodium acetate afforded 3-methyl-4-(pyridin-4'-yl)-5-dihydro-1, 2, 4-triazin-6-(1*H*) one (XXVa), while treatment of XXIVb with *p*-nitrobenzoyl chloride in the presence of pyridine-ethanol yieled 3-(*p*-nitrophenyl)-4-(pyridin-4'-yl)-5-dihydro-1,2,4-triazin-6-(1*H*) one. (XXVb). The structures of XXVa, b were based upon elemental analysis and spectral data. Their IR spectra showed absorption bands due to ketonic ring and amino group, while ^{1}H-NMR spectrum of XXVb showed the signals due to CH_2, NH, aryl and pyridine protons.

Finally, the alkylation of compound II using 1, 1'-dichloroacetic acid in DMF yielded amino derivative XXVI, which on addition of mercaptoacetic acid followed by cyclization in dry benzene [13], 2-carboxy-3-(pyridin-4'-yl) thiazolidin-4-one (XXVII) was obtained. The structure of XXVII was established from elemental analysis and spectral data: (i) IR specrum showed the presence of characteristic bands due to C=O and CH_2 groups, with the disappearance of exocyclic C=N band, (ii) UV spectrum showed λ_{max} due to n-π* and π-π* and (iii) ^{1}H-NMR spectrum recorded the presence of signals which is attributed to CH_2, CH, pyridine and OH protons.

Antibacterial an antifungal activities. The prepared compounds IV-XXVII were tested for their antibacterial activity against *Bacilus subtilis* and antifungal activity against *Aspergillus terreus* by the disc method [14]. The compounds were tested at concentration 100 μg/ml in DMF and were compared with that of the reference control [15]. The results showed no bactericidal effect and had a promoting effect towards the bacterial growth, especially in the case of compounds VI, XVIII and XXVI.

On the other hand, the compounds VI, XVIII and XXVI showed moderate activity against the tested fungi. Therefore, it is clear that these compounds had promoting growth effect on *BacilLus subtilis* and inhibition effect on *Aspergillus terreus.*

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