Chapter VI

Synthesis of Novel Bis-(5-isonicotinoyl-1,2,3,4-tetrahydropyrimidines)

Introduction

Heterocyclic compounds containing isonicotinoyl group are well documented in the literature\textsuperscript{1-6}. Literature survey reveals that compounds containing isonicotinoyl groups have been synthesized and were tested for their chelating\textsuperscript{7-10} and biological properties\textsuperscript{11-14}. Isonicotinic acid hydrazide (isoniazid) is reported to be a well-acknowledged drug\textsuperscript{15-16} and is one of the primary drugs used in combination with ethanbutol, rifampin, streptomycin and pyrazinamide to treat tuberculosis\textsuperscript{17}. A large number of compounds containing the isoniazid moiety have been synthesized, tested and further studies are going on due to the increasing resistance of bacterial strains of certain type of antibiotics\textsuperscript{18-19}.

6.1 The synthesis and biological properties of a few such molecules are described in the following sections.

6.1.1 S. Schenone and coworkers have reported\textsuperscript{20} the synthesis of a series of 1,3,4-thiadiazol-2(3\textit{H})-ones with a nicotinoyl/isonicotinoyl group in position 3 and an arylamino substituent in position 5 of the ring as shown in Scheme 1. Reaction of nicotinoyl or isonicotinoyl hydrazide (1) with the relevant acylisothiocyanates (2) gave the corresponding acylthiosemicarbazides (3). Subsequent cyclization with phosgene, in the presence of sodium acetate led to the expected 1,3,4-thia-diazol-2(3\textit{H})-ones (4). These compounds were evaluated for antipyretic and anti-inflammatory activities. All the compounds exhibited anti-inflammatory activity and were devoid of antipyretic properties. It was also observed that the best results were obtained in the isonicotinoyl compounds and the furoyl substituent showed superior influence over the benzoyl group.
6.1.2 M. G. Mamolo and coworkers have also reported\textsuperscript{21} the synthesis of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole derivatives as shown in Scheme 2.
The synthesis of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazoles (9) was carried out by reacting isonicotinoyl chloride with the corresponding 5-aryl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazoles (8) which in turn were prepared from the corresponding 3-aryl-1-(pyridin-2-yl)-propenones (7) by treating them with hydrazine hydrate. The required propenones were synthesized by the reaction of the appropriate aromatic aldehyde (5) with 2-acetylpyridine (6). It was further observed that the pyrazoles (8) were quite unstable and in many cases the crude residue was further reacted to give the final compounds. These compounds were tested for their in vitro antimycobacterial activity. These compounds were tested for their antimycobacterial activity towards a strain of Mycobacterium tuberculosis H37Rv and towards a strain of M. tuberculosis H4, isolated from human bronchial aspirates. The activity of these compounds towards strains of M. gordonae, M. bovis, Candida albicans, Escherichia coli and Staphylococcus epidermis was also determined. These compounds showed interesting activity against a strain of Mycobacterium tuberculosis and a human strain of M. tuberculosis H4.
6.1.3 P. Ponka and coworkers have reported\textsuperscript{22} the synthesis of a series of acylhydrazone by schiff base condensation of various acyl hydrazide (including isonicotinic acid hydrazide) with aromatic aldehydes like pyridoxal (10), salicylaldehyde (13) and 2-hydroxy-1-naphthaldehyde (15) to give various acyl hydrazones (11, 14, 16). (Scheme 3). Compounds of complex 12 types have shown varying abilities to promote the movement of iron across biological membrane.

Later Ponka and Buss reported\textsuperscript{23} the hydrolysis of pyridoxal isonicotinoyl hydrazone (PIH) and its analogues. These PIH were synthesized by previously reported methods\textsuperscript{24-28} and it was found that PIH analogues undergo significant amino acid-catalysed hydrolysis in cell culture medium and in serum, achieving equilibrium with their corresponding aldehydes and hydrazides with half-times of 1-8hrs. These along with other data led to the conclusion that PIH analogs effectively mobilize iron in vivo and in vitro, and could therefore be promising candidates for treatment of the secondary iron overload.
Scheme 3
6.1.4 In an attempt to develop chelators as potent anti-tumor agents, D. R. Richardson and coworkers reported\textsuperscript{29} the synthesis of two series of novel ligands based on the very active 2-pyridylcarboxaldehyde isonicotinoyl hydrazone (PCIH) group. They replaced the aldehyde moiety of the PCIH series (17) with more lyophylic 2-quinoline carboxaldehyde or di-2-pyridylketone moieties giving 2-quinolinecarboxaldehyde isonicotinoyl hydrazone (QCIH) series (18) and di-2-pyridylketone isonicotinoyl hydrazone (PKIH) series (19).

![Chemical structures of PCIH, QCIH, and PKIH](image)

The PCIH (17) and QCIH (18) analogues were synthesized by Schiff base condensation with either 2-pyridylcarboxaldehyde or 2-quinolinecarboxaldehyde and their respective acid hydrazide\textsuperscript{30}. The PKIH series (19) were synthesized by condensing 2-di-pyridyl ketone with the acid hydrazide\textsuperscript{31}. They examined the structure-activity relationship of the 18 ligands belonging to the three related groups of novel aroyl hydrazone chelators as shown above. It was observed that despite each of these analogs having similar Fe-binding site, the activity of these chelators differed substantially. The PCIH group of ligands had high Fe chelation activity but low antiproliferative effects. The QCIH group had little Fe chelation or
antiproliferative activity, and some of the PKIH series were amongst the most effective Fe chelators and antiproliferative agents. Later Des R. Richardson and coworkers reported\(^3\) the measurement of redox activity of iron in the presence of the di-2-pyridyl ketone isonicotinoyl hydrazone series of chelators using a variety of assays. The results of the investigation demonstrated that the antiproliferative activity of these chelators relates to intracellular iron chelation, followed by the stimulation of iron-mediated free radical generation via the so-formed complex.

6.1.5 M. J. Hardie and coworkers reported\(^3\) the synthesis of a range of new multidentate bridging ligands/molecular hosts by appending nitrogen-containing heterocycles to either cyclotricatechylene or cyclotriguaiacylene cores. For example, they reported the synthesis of tris(isonicotinoyl)cyclotriguaiacylene (21) which was prepared by stirring cyclotriguaiacylene (20) and nicotinoyl hydrochloride at room temperature in THF (Scheme 4).

![Scheme 4](image)

6.1.6 Alan R. Katritzky and coworkers have reported\(^3\) the synthesis of N-acylsulfonamides. These preparations were carried out by reacting N-acetylbenzotriazoles (22) with sulfonamides (methylsulfonamide (23), p-
tolylsulfonamide (25) and acetazolamide (28)) in THF in the presence of NaH for 90 minutes. Removing THF gave the sodium salt of the corresponding N-acylsulfonamides, which on acidification with 2N HCl solution gave N-acylsulfonamides in good yield. For example, N-isonicotinoylmethanesulfonamide (24) and N-isonicotinoyl-4-methylbenzenesulfonamide (26) were synthesized as shown in Scheme 5.

They also reported the synthesis of N-acylsulfonamides derived from acetazolamide. For example, N-\{5-[(isonicotinoylamo)sulfonyl]-1,3,4-thiadiazol-2-yl\}acetamide (28) was synthesized as shown in Scheme 6.
They also reported the synthesis of N-acylsulfonamides by utilizing sulfonylbenzotriazole (29) and amides (reverse reaction). The reverse synthesis of N-isonicotinoylmethanesulfonamide (24) is shown in Scheme 7.

6.1.7 Considering the importance of isonicotinic acid hydrazide (isoniazid), pyrazoles and alkoxyphthalamides in industrial and pharmacological fields, G.L. Talesara and coworkers reported the synthesis and pharmacological studies of some 1-isonicotinoyl-3-methyl-4-(4-substituted phenyl)-3a,4-dihydropyrazolo[3,4-c]pyrazoles and their ethoxyphthalamide derivatives, where they undertook the synthesis of some new combinatorial molecules, incorporating above moieties with the aim to increase their biological activities. When isoniazid (1) was reacted with ethylacetoacetate in absolute alcohol 2-isonicotinoyl-5-methyl-2,4-dihydro-3H-pyrazol-3-one (30) was obtained. This was then reacted with various 4-substituted benzaldehydes to obtain their corresponding arylidene derivatives (31), which were then subjected to reaction with hydrazine hydrate. This led to a cyclocondensation
reaction yielding 4-(4-chlorophenyl/4-methoxyphenyl/4-N,N- 
dimethylaminophenyl/phenyl)-1-isonicotinoyl-3-methyl-3a,4-dihydropyrazolo[3,4- 
c]-pyrazole (32) (Scheme 8). These compounds were tested for their antimicrobial 
activity against one-gram positive *B. Subtilis* and three-gram negative strains, *P. 
mirabilis*, *E. coli* and *K. pneumoniae*. For comparative study two standard drugs 
ciprofloxacin and roxithromycin were used. *Candida albicans* (MTCC227) and 
*Aspergillus fumigatus* (MTCC2550) were used as the testing fungal strains. 
Amphotericin B and flucanazole were used as standard drugs. However, the overall 
activity profile of the compounds were found to be moderate to poor.

With an aim to increase the antimicrobial activity of these molecules they (Talesara 
et al.) fused the ethoxyphthalimide moiety with the pyrazolo[3,4-c]pyrazole ring 
system. Thus, when compound 32 was reacted with phthalimidoxyethyl bromide 
(35) in ethanol in the presence of pyridine, 2-N-ethoxyphthalimido-6-isonicotinoyl-
4-methyl-3-(4-substituted phenyl)-3,3a-dihydro pyrazolo[3,4-c]pyrazoles (36) were 
obtained (Scheme 9).
Scheme 8
These compounds 36 showed comprehensive fungus-inhibiting properties than bacterial. Two compounds showed strong activity against *P. mirabilis*, *B. subtilis*, *C. albicans* and *A. fumigatus* while moderate to good activity against *K. pneumoniae* and *E. coli*. The antiproliferative activity was measured against murine leukemia cells (LI210/0) and human T-lymphocyte cells (Molt 4/C8, CEMO/0 cells). However none of the compounds exhibited antitumor cell activity at a reasonably low concentration. They also reported the antiviral activity of these compounds but none of the compounds was able to inhibit the cytopathic effects of influenza A or B at subtoxic concentration or at the highest concentration (100 μg/mL) tested.

Later G.L. Talesara and coworkers reported the synthesis of 6-N-ethoxyphtalimido-2-isonicotinoyl-4-methyl-3-(4-substituted phenyl)-3,3a-dihydro pyrazolo[3,4-c]pyrazoles (40) (Scheme 10).
They used 5-methyl-2,4-dihydro-3H-pyrazol-3-one (37) as starting material which was prepared by the reaction between ethylacetoacetate and hydrazine hydrate in absolute alcohol. Compound 37 on condensation with substituted benzaldehydes in the presence of sodium acetate as a base gave the corresponding 5-methyl-4-substituted benzyldene-2,4-dihydro-3H-pyrazol-3-one (38). These, when reacted with phthalimidoxyethyyl bromide (35) in acetone using K₂CO₃ as a base afforded 1-N-ethoxyphthalimido-3-methyl-4-(4-substituted benzyldene) pyrazol-5-one (39). Compound 39 was cyclized with isoniazid in the presence of sodium acetate and acetic acid to yield 6-N-ethoxyphthalimido-2-isonicotinoyl-4-methyl-3-(4-substitutedphenyl)-3,3a-dihydropyrazolo[3,4-c]pyrazoles (40).
6.1.8 H.G. Bonacorso and coworkers have reported\cite{Bonacorso1986} the synthesis of a novel series of heteroaryl-2-pyrazolines trihalomethyl and substituted heteroaryl as non-condensed heteropolycyclic systems. The regiospecific cyclocondensation reaction of 1,1,1-trifluoro(chloro)-4-methoxy-4-(2-furyl)-3-buten-2-ones and 1,1,1-trifluoro(chloro)-4-methoxy-4-(2-thienyl)-3-buten-2-ones (41) with isonicotinic acid hydrazides in anhydrous methanol under mild conditions at room temperatures yielded 3-(2-furyl)- or 3-(2-thienyl)-5-hydroxy-5-trifluoro(chloro)methyl-4,5-dihydro-1H-1-(isonicotinoyl)pyrazoles (42) (Scheme 11).

![Scheme 11](image)

6.1.9 J. Quiroga and coworkers\cite{Quiroga2019} in continuation of their study on the preparation of amino derivatives of pyrazoles, by the reaction of β- aminoacrylonitriles with compounds containing hydrazine moiety, reported the reaction of isoniazid with β-aminoacrylonitrile in the presence of sodiumacetate trihydrate in ethanol under refluxing conditions. Under these conditions, N,N'-bis-(isonicotinoyl)hydrazine (44) was obtained with the elimination of a hydrazine molecule instead of the expected pyrazole (43) (Scheme 12).
Prompted by the above literature reports and also by the potential biological activities of 5-nitro-1,2,3,4-tetrahydropyrimidine derivatives of the type 45\textsuperscript{18} and 46\textsuperscript{49} and in continuation with our work on the synthesis of bis-heterocycles (especially tetrahydropyrimidines) we envisaged that the presence of another electron withdrawing group in position 5 of the tetrahydropyrimidine ring could have an important impact on the biological activities of these molecules. Our literature survey revealed that 1,2,3,4-tetrahydropyrimidine and bis-(1,2,3,4-tetrahydropyrimidines) bearing isonicotinoyl group in position 5 of the ring are unknown in the literature to the best of our
knowledge and hence their biological properties remain unexplored.

Furthermore, bis-compounds have received considerable importance as being model for main chain polymers\textsuperscript{50-54}. It is also reported that many biologically active natural and synthetic products have molecular symmetry\textsuperscript{55}. As a result, a number of organic chemists are shifting their attentions to the synthesis of bis-heterocycles\textsuperscript{56-59}. Prompted by the above facts, we undertook to develop synthetic methodologies for bis-(5-isonicotinyl-1,2,3,4-tetrahydropyrimidines) and the results of our studies are reported herein.

6.2 In order to synthesize the proposed bis-1,2,3,4-tetrahydropyrimidine bearing isonicotinyl group in position 5 of the ring, we required enaminoles of the type 48 which could be derived from 4-acetylpyridine (Scheme 13).

![Scheme 13](image-url)
Their synthesis could be achieved by first reacting 4-acetylpyridine with DMF-DMA following previously reported procedure\textsuperscript{60} to yield the formylated product 47 and then converting 47 into 48 by a procedure\textsuperscript{61} developed in our laboratory. The structures of 48 as 3-(phenyl/benzyl/methyl)amino-1-isonicotinoylpropenones were established with help of spectral and analytical data. The enamiones 48a-c exist exclusively in Z-form as indicated by the highly deshielded N-H proton (10.76-12.25 ppm) signals due to hydrogen bonding and the low coupling constants of the vinylic protons (J=6 Hz).

6.3 These heteroaroyl enamiones (48) thus synthesized were used as synthons for the construction of the required bis-1,2,3,4-tetrahydropyrimidines as shown in Scheme 14.
6.4 Results and discussions.

Thus, when 48a (2 mmol) was reacted with a mixture of ethylenediamine (1 mmol) and formaldehyde (4 mmol) in methanol, expected product 49a was obtained in 55% yields, the structure of which was established to be [3,3’-(ethane-1,2-diyl)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis(pyridin-4-ylmethanone) based on
spectral and analytical data. The reaction of 48\(a\) with other diamines (\(A= -\text{CH}_2\text{CH}_2\text{CH}_2-,\ -\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-,\ -\text{C}_6\text{H}_4-\)) and formaldehyde led to the formation of the respective products 49\(b-d\) in 60-65\% yields. Likewise, 48\(b\) and 48\(c\) reacted with diamines and formaldehyde under similar conditions giving the expected products 49\(e-i\) in good yields. The infrared spectra of 49\(a-o\) showed strong peaks in the region of 1500 to 1630 cm\(^{-1}\) due to extensively delocalised double bonds and carbonyl groups. In the \(^1\text{H}\) NMR spectra of 49\(a-o\), the \(\alpha\) and \(\beta\) protons of pyridine ring appear as doublets in the vicinity of 8.60 and 7.30 ppm respectively. The signal of \(\text{C}_6\text{H}\) proton of the THP ring remains buried with the aromatic protons except in case of 49\(k-o\), where it was found resonating at 6.97 ppm. The signals due to benzylic \(\text{CH}_2\) protons in 49\(f-j\) were found in the range of 3.65-3.90 ppm. The protons at C-4 of the THP ring resonated just below 4.00 ppm except in cases where phenyl or biphenyl group is attached to N-3, while those bonded to C-2 were more de-shielded and resonated in the vicinity of 4.50 ppm. The N-\(\text{CH}_2\) protons of the linker chain of 49\(a-c, e-g, i-k\) resonated between 2.40 to 2.80 ppm, while other \(\text{CH}_2\) protons of the linker chains appeared as multiplets close to 1.75ppm. In the \(^{13}\text{C}\) NMR spectra of the THPs, the most striking signal was due to carbonyl carbon close to 190 ppm. The \(^1\text{H}\) NMR and \(^{13}\text{C}\) NMR Spectra of \([3,3'-(\text{propane}-1,3-\text{diyl})\text{bis}(1-\text{phenyl}-1,2,3,4-\text{tetrahydropyrimidine}-5,3-\text{diyl})\text{bis(pyridin-4-ylmethane})\) 49\(b\) are shown in pages 239-240.
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| F1     | 13890 25 Hz |
| F2P    | -1 870 ppm |
| F2     | -126 00 Hz |
| PPMCM  | 99480 999 cm |
| Hz/cm  | 750 81323 Hz/cm |

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![Chemical Structure](image)
6.5 Conclusion.

In conclusion, we have synthesized a series of hitherto unknown bis-(5-isonicotinoyl-1,2,3,4-tetrahydropyrimidines) in good yields, from the respective enaminones derived from 4-acetyl pyridine, wherein we have succeeded in replacing the nitro group at the 5-position of the THP ring by another electron withdrawing group. The anti-bacterial properties of these bis-tetrahydropyrimidines are currently under investigation.

6.6 Experimental Section.

Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 983 spectrometer. $^1$H NMR and $^{13}$C NMR (300 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to TMS as internal reference. FAB-mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 Mass spectrometer using Argon as the FAB gas and m-nitrobenzylalcohol as the matrix. Elemental analyses were performed on a Vario-EL III instrument. Enaminones 48 were synthesized by our reported procedure $^{61}$.

6.7 General procedure

6.7.1 Synthesis of 3-phenylamino-1-pyridin-4-ylpropenone (48a).

To a solution of enaminone 47 (1 mmol) in 2 ml acetic acid aniline (1 mmol) was added and the resulting mixture was stirred at room temperature for 45 hours when a solid product precipitated out. After the completion of the reaction (monitored by TLC), the mixture was poured over chilled water and the precipitated product was collected by filtration, washed repeatedly by water to ensure complete removal of acid and dried to give practically pure 48a in 82% yields. It was recrystallised from hexane-ethyl acetate mixture.
6.7.2 Synthesis of 3-benzylamino-1-pyridin-4-ylpropenone (48b).

To a solution of enaminone 47 (1 mmol) in 3 ml ethanol was added benzylamine (1.2 mmol) and the resulting mixture was refluxed for 48 hours. After the completion of the reaction (monitored by TLC), ethanol was distilled off to give a gum, which on trituration with hexane yielded practically pure 48b in 61% yield. It was recrystallised from hexane-ethylacetate mixture. Alternatively this compound 48b could also be synthesized under microwave irradiation. A mixture of enaminone 47 (1 mmol) and benzylamine (1.5 mmol) was taken in a 5-mL conical flask and the resulting mixture was irradiated in domestic microwave oven at 300 watt for an appropriate time. At the end of the reaction (monitored by TLC), the flask was cooled and the mass was triturated with hexane to give the desired product 48b, which was recrystallized from hexane-ethylacetate mixture.

6.7.3 Synthesis of 3-methylamino-1-pyridin-4-ylpropenone (48c).

To a solution of enaminone 47 (1 mmol) in 3 ml ethanol was added an aqueous solution of methylamine (3 mmol, 40% solution) and the resulting mixture was stirred at 50°C for 40 hours. After the completion of the reaction (monitored by TLC), ethanol was distilled off to give a brown gum, which was dissolved in chloroform (3 ml). This solution was washed with water (2x2 ml), dried over anhydrous sodium sulphate and chloroform distilled off to give the product 48c in 52% yields. It was further purified by column chromatography (silica gel, 20% ethylacetate-hexane). Alternatively 48c could also be synthesized under microwave irradiation. A mixture of 47 (1 mmol) and methylamine (3 mmoles) was taken in a 5ml conical flask and the resulting mixture was irradiated in domestic microwave oven at 100 watt for appropriate time. After the completion of the reaction (monitored by TLC),
chloroform (3 ml) was added and the organic layer was washed with water (2x2 ml), dried over anhydrous Na$_2$SO$_4$ and the solvent removed to obtain the enaminone 48c which was further purified by column chromatography (silica gel, 20% ethylacetate-hexane).

**6.8 Synthesis of Bis-tetrahydropyrimidines (49a-o).**

A mixture of diamine (0.5 mmol) and formaldehyde (2 mmol) in 1 ml of methanol was stirred at room temperature for 5-10 minutes. To this was added a solution of the enaminone 48 (1 mmol) in 4 ml of methanol and the resulting solution was refluxed for 4-12 hours. On completion of the reaction (monitored by TLC), the solvent was distilled off. The residue was dissolved in 3 ml of chloroform and the solution washed with water (2x2 ml), dried over anhydrous Na$_2$SO$_4$ and chloroform distilled off to give a gum from which the product 49 was isolated by column chromatography (silica gel, ethylacetate) in 40-65% yields.

**6.9 Individual description of the compounds.**

(Z) 3-phenylamino-1-pyridin-4-ylpropenone 48a.

![Chemical structure of 48a](attachment:image.png)

This compound was obtained as a yellow solid, mp 149-150°C; IR (KBr): 1566, 1639, 3032, 3217 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 6.02 (d, 1H, J=6Hz), 7.13-7.16 (m, 3H), 7.36-7.41 (m, 2H), 7.61 (dd, 1H, J=6Hz, 12Hz), 7.73 (d, 2H, J=6Hz), 8.76(d, 2H,
J=6Hz), 12.25 (br d, 1H, exchangeable with D₂O J=12Hz); MS: (m/z) 224 [M⁺], 225 [MH⁺]; Anal. Calcd. for C₁₄H₁₂N₂O (224.26): C, 74.98; H, 5.39; N, 12.49%. Found: C, 74.75; H, 5.50; N, 12.42%.

(E) 3-benzylamino-1-pyridin-4-ylpropenone 48b.

This compound was obtained as a light brown solid, mp 113-115°C; IR (KBr): 1566, 1639, 3025, 3443 cm⁻¹; ¹H NMR (CDCl₃): δ 4.49 (d, 2H, J= 6Hz), 5.74 (d, 1H, J=6Hz), 7.10 (dd, 1H, J=6 Hz, 12.9 Hz), 7.27-7.39 (m, 5H), 7.66 (d, 2H, J=5.7Hz), 8.68 (d, 2H, J=5.7Hz), 10.76 (br d, 1H, exchangeable with D₂O); ¹³C NMR (CDCl₃): δ 52.9, 90.6, 120.7, 127.3, 128.0, 128.9, 137.1, 146.1, 150.3, 155.2, 187.7; MS: m/z 238 [M⁺], 239 [MH⁺]; Anal. Calcd. for C₁₅H₁₄N₂O (238.28): C, 75.61; H, 5.92; N, 11.76%. Found: C, 75.85; H, 6.01; N, 11.82%.

(Z) 3-methylamino-1-pyridin-4-ylpropenone 48c.

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This compound was obtained as light brown gum, IR (KBr): 1527, 1566, 1639, 3005, 3244 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 3.15 (d, 3H, J=6Hz), 5.90 (d, 1H, J=7.5Hz), 7.30 (dd, 1H, J=7.5, 12Hz), 7.95 (d, 2H, J=6Hz), 9.10 (d, 2H, J=6Hz), 11.01 (br d, 1H, exchangeable with D$_2$O); *Anal. Calcd.* for C$_9$H$_{10}$N$_2$O (162.19): C, 66.65; H, 6.21; N, 17.27%. *Found:* C, 66.51; H, 6.28; N, 17.36%.

[3,3'-(Ethane-1,2-diyl)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49a.

![Chemical structure of 49a]

This compound was obtained as a white solid in 55% yield, mp 189-191$^\circ$C; IR (KBr): 1541, 1596, 1649 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 2.80 (s, 4H), 3.83 (s, 4H), 4.64 (s, 4H), 6.92 (d, 4H), 7.15-7.20 (m, 2H), 7.27-7.51 (m, 10H), 8.69 (d, 4H); MS: m/z 557 [MH$^+$]; *Anal. Calcd.* for C$_{34}$H$_{32}$N$_6$O$_2$ (556.66): C, 73.36; H, 5.79; N, 15.10%. *Found:* C, 73.55; H, 5.73; N, 15.02%.

[3,3'-(Propane-1,3-diyl)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49b.

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This compound was obtained as a white solid in 65% yield, mp 193-195°C; IR (KBr): 1495, 1568, 1641 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.75-1.82 (m, 2H), 2.68 (t, 4H), 3.78 (s, 4H), 4.54 (s, 4H), 6.93 (d, 4H) 7.13-7.18 (m, 2H), 7.27-7.50 (m, 10H), 8.69 (d, 4H); \(^13\)C NMR (CDCl\(_3\)): \(\delta\) 26.3, 47.3, 50.3, 68.4, 108.9, 118.6, 122.3, 124.9, 129.8, 144.0, 146.0, 146.8, 150.0, 191.2; \textit{Anal. Calcd. for C\(_{35}\)H\(_{34}\)N\(_6\)O\(_2\) (570.68): C, 73.66; H, 6.01; N, 14.73%. Found: C, 73.81; H, 6.09; N, 14.81%.

\[3,3'-(\text{Butane-1,4-diyl})\text{bis}(1\text{-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl})\text{bis-}(\text{pyridin-4-y}l\text{methanone})\] 49c.

This compound was obtained as light yellow solid in 60% yield, mp 153-154°C; IR (KBr): 1498, 1568, 1633 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.60-1.61 (m, 4H), 2.59-2.60 (m, 4H), 3.79 (s, 4H), 4.54 (s, 4H), 6.93 (d, 4H), 7.14-7.18 (m, 2H), 7.27-7.45 (m, 10H), 8.69 (d, 4H); MS: m/z 585 [MH\(^+\)]; \textit{Anal. Calcd. for C\(_{36}\)H\(_{36}\)N\(_6\)O\(_2\) (584.71): C, 73.95; H, 6.21; N, 14.37%. Found: C, 73.83; H, 6.25; N, 14.32%.

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[3,3’-(1,4-Phenylene)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49d.

This compound was obtained as a yellow solid in 62% yield, mp 168-170°C; IR (KBr): 1563, 1619, 1655 cm⁻¹; ¹H NMR (CDCl₃): δ 4.39 (s, 4H), 5.08 (s, 4H), 6.87-6.93 (m, 4H), 7.15-7.46 (m, 16H), 8.68 (d, 4H, J=5.4Hz); MS: m/z 605 [MH⁺]; Anal. Calcd for C₃₈H₃₂N₆O₂ (604.7): C, 75.48; H, 5.33; N, 13.90%. Found: C, 75.31; H, 5.38; N, 13.84%.

[3,3’-(Biphenyl-4,4’-diyl)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49e.

This compound was obtained as a brown solid, yield 50%, mp 230°C (decomp); IR (KBr): 1567, 1654 cm⁻¹; ¹H NMR (CDCl₃): δ 4.51 (s, 4H), 5.19 (s, 4H), 6.94-7.00
(m, 12H), 7.16-7.89 (m, 12H), 8.68 (d, 4H, J=4.8Hz); $^{13}$C NMR (CDCl$_3$): δ 45.2, 65.0, 104.2, 119.2, 120.5, 122.3, 124.6, 125.1, 126.3, 127.0, 129.7, 142.8, 146.2, 149.5, 151.0, 189.5; Anal. Calcd. for C$_{44}$H$_{36}$N$_6$O$_2$ (680.8): C, 77.63; H, 5.33; N, 12.34%. Found: C, 77.47; H, 5.39; N, 13.28%.

[3,3’-(Ethane-1,2-diyl)bis(1-benzyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49f.

\[
\text{O} \quad \text{N} \quad \text{N} \quad \text{O}
\]

This compound was obtained as a light brown gum in 45% yield, IR (KBr): 1561, 1656 cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 2.55 (s, 4H), 3.63 (s, 4H), 3.98 (s, 4H), 4.27 (s, 4H), 7.18-7.32 (m, 16H), 8.65 (d, 4H); $^{13}$C NMR (CDCl$_3$): δ29.5, 46.9, 50.5, 58.2, 67.3, 104.9, 121.0, 122.3, 127.6, 128.4, 129.0, 147.3, 150.5, 189.7; Anal. Calcd. for C$_{36}$H$_{36}$N$_6$O$_2$ (584.71): C, 73.95; H, 6.21; N, 14.37%. Found: C, 73.99; H, 6.26; N, 14.41%.

[3,3’-(Propane-1,3-diyl)bis(1-benzyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49g.

\[
\text{O} \quad \text{N} \quad \text{N} \quad \text{O}
\]
This compound was obtained as a light brown gum in 45% yield, IR (KBr): 1563, 1656 cm⁻¹; ¹H NMR (CDCl₃); δ 1.42-1.52 (m, 2H), 2.40 (t, 4H), 3.61 (s, 4H), 3.86 (s, 4H), 4.27 (s, 4H), 7.17-7.19 (m, 6H), 7.32-7.37 (m, 10H), 8.63 (d, 4H); ¹³C NMR (CDCl₃): δ 25.6, 47.0, 50.4, 51.8, 58.1, 66.4, 105.0, 121.0, 122.2, 127.4, 128.5, 128.9, 147.3, 149.6, 189.5; Anal. Calcd. for C₃₇H₃₈N₆O₂ (598.74): C, 74.22; H, 6.40; N, 14.04%. Found: C, 74.05; H, 6.43; N, 14.11%.

[3,3′-(Butane-1,4-diyl)bis(1-benzyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49h.

This compound was obtained as a light brown gum in 50% yield, IR (KBr): 1563, 1659 cm⁻¹; ¹H NMR (CDCl₃); δ 1.25-1.33 (m, 4H), 2.34-2.41 (m, 4H), 3.64 (s, 4H), 3.93 (s, 4H), 4.27 (s, 4H) 7.15-7.35 (m, 16H), 8.67 (d, 4H); MS: m/z 612 [M⁺]; Anal. Calcd. for C₃₈H₄₀N₆O₂ (612.76): C, 74.48; H, 6.58; N, 13.71%. Found: C, 74.31; H, 6.54; N, 13.77%.
[3,3'-(1,4-Phenylene)bis(1-benzyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis(pyridin-4-ylmethanone) 49i.

This compound was obtained as a brown solid in 40% yield, mp 188-190°C; IR (KBr): 1566, 1654 cm⁻¹; \(^1\)H NMR (CDCl₃): δ 4.27 (s, 4H), 4.30 (s, 4H), 4.52 (s, 4H), 6.74 (s, 4H), 7.05-7.15 (m, 6H), 7.21-7.35 (m, 10H), 8.66 (d, 4H); MS: m/z 632 [M⁺], 633 [MH⁺]; \(\text{Anal. Calcd. for } C_{40}H_{36}N_6O_2 (632.75): C, 75.93; H, 5.73; N, 13.28\%.
\(\text{Found: } C, 75.72; H, 5.69; N, 11.32\%.

[3,3'-(Biphenyl-4,4-diyl)bis(1-benzyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49j.

This compound was obtained as a brownish solid in 45% yield, mp 225°C (decomp); IR (KBr): 1565, 1653 cm⁻¹; \(^1\)H NMR (CDCl₃): δ 4.32 (s, 4H), 4.38 (s, 4H), 4.64 (s, 4H), 6.90 (s, 4H), 7.09-7.15 (m, 6H), 7.26-7.41 (m, 14H), 8.66 (d, 4H); Mass (m/z)
708, 709 [MH⁺]; Anal. Calcd. for C₄₆H₄₀N₆O₂ (708.85): C, 77.94; H, 5.69; N, 11.86%. Found: C, 77.74; H, 5.64; N, 11.90%.

[3,3'-(Ethane-1,2-diyl)bis(1-methyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis(pyridin-4-ylmethanone) 49k.

This compound was obtained as a light brown gum in 45% yield, IR (KBr): 1565, 1654 cm⁻¹; ¹H NMR (CDCl₃): δ 2.64 (s, 4H), 3.02 (s, 6H), 3.35 (s, 4H), 3.41 (s, 4H), 6.85 (s, 2H), 7.40 (d, 4H), 8.66 (d, 4H); ¹³C NMR (CDCl₃): δ 40.00, 45.11, 53.52, 70.05, 84.82, 106.25, 122.36, 149.60, 151.50, 189.93; Anal. Calcd. for C₂₄H₂₂N₆O₂ (432.52): C, 66.65; H, 6.53; N, 19.43%. Found: C, 66.81; H, 6.57; N, 19.50%.

[3,3'-(Propane-1,3-diyl)bis(1-methyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis(pyridin-4-ylmethanone) 49l.

This compound was obtained as a light brown gum in 55% yield, IR (KBr): 1560, 1655 cm⁻¹; ¹H NMR (CDCl₃): δ 1.74-1.78 (m, 2H), 2.64 (t, 4H), 2.98 (s, 6H), 3.31 (s,
4H), 3.48 (s, 4H), 6.97 (s, 2H), 7.33 (d, 4H), 8.66 (d, 4H); $^{13}$C NMR (CDCl$_3$): δ 26.13, 41.21, 46.53, 50.95, 68.86, 104.95, 122.33, 149.63, 150.25, 151.20, 189.20; Anal. Calcd. for C$_{25}$H$_{30}$N$_6$O$_2$ (446.54): C, 67.24; H, 6.77; N, 18.82%. Found: C, 67.15; H, 6.75; N, 18.91%.

[3,3’-(Butane-1,4-diyl)bis(1-methyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis(pyridin-4-ylmethanone) 49m.

![Structure of 49m]

This compound was obtained as a light brown gum in 60% yield, IR (KBr): 1563, 1655 cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 1.58-1.73 (m 4H), 2.38-2.57 (m, 4H), 2.96 (s, 6H), 3.74 (s, 4H), 3.95 (s, 4H), 6.96 (s, 2H), 7.32 (d, 4H), 8.70 (d, 4H); MS: m/z 461 [MH$^+$]; Anal. Calcd. for C$_{26}$H$_{32}$N$_6$O$_2$ (460.57): C, 67.80; H, 7.06; N, 18.25%. Found: C, 67.98; H, 7.06; N, 18.21%.

[3,3’-(1,4-Phenylene)bis(1-methyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis(pyridin-4-ylmethanone) 49n.

![Structure of 49n]

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This compound was obtained as a light brown solid in 40% yield, mp 235°C; IR (KBr): 1615, 1654 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.01 (s, 6H), 4.25 (s, 4H), 4.59 (s, 4H), 6.95-6.99 (m, 6H), 7.32-7.33 (m, 4H), 8.64-8.70 (m, 4H); \(^13\)C NMR (CDCl\(_3\)): \(\delta\) 40.7, 45.1, 66.6, 105.2, 118.8, 121.9, 142.6, 146.9, 149.4, 151.7, 188.40; \textit{Anal. Calcd. for C\(_{28}\)H\(_{28}\)N\(_6\)O\(_2\) (480.56):} C, 69.98; H, 5.87; N, 17.49%. \textit{Found:} C, 69.85; H, 5.90; N, 17.61%.

[3,3’-(Biphenyl-4,4’-diyl)bis(1-methyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis- (pyridin-4-ylmethanone) \(490\)

This compound was obtained as an off white solid in 40% yield, mp 235°C; IR (KBr) 1563, 1654 cm\(^{-1}\); \(^1\)HNMR (CDCl\(_3\)): \(\delta\) 3.02 (s 6H), 4.36 (s, 6H), 4.67 (s, 6H), 6.95-7.07 (m, 6H), 7.26-7.38 (m, 4H), 7.45-7.51 (m, 4H), 8.65-8.66 (m, 4H); Mass (m/z) 556 [M\(^+\)], 557 [M\(^{+}\)H\(^+\)]; \textit{Anal. Calcd. for C\(_{34}\)H\(_{32}\)N\(_6\)O\(_2\) (556.66):} C, 73.36; H, 5.79; N, 15.10%. \textit{Found:} C, 73.21; H, 5.82; N, 15.29%.
6.10 References.


35) Govt. of India, Ministry of Health and Family Welfare; Indian Pharmacopoeia., 1996, 408.


