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Research Article

DESIGN, SYNTHESIS, MOLECULAR DOCKING, QSAR, ANTIBACTERIAL ACTIVITY STUDIES OF NOVEL TETRAHYDROCARBAZOLE DERIVATIVES

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A B S T R A C T

The heterocyclic compound tetrahydrocarbazole and its derivatives are reported to possess varied biological activities.. The enzyme, namely GlcN-6-P synthase, (L-glutamine: D-fructose-6P amidotransferase, PDB CODE:1XFF), also known under the trivial name of glucosamine-6-phosphate synthase, is a new target for antimicrobials. It is a protein synthesis inhibitor in bacteria. It binds to a small 16s rRNA of the 30s subunit of the bacterial ribosome interfering with the binding of formyl – methionyl - tRNA to the 30s subunit. The present investigations is aimed to synthesize some new 1,2,3,4-tetrahydrocarbazoles and further to evaluate them for their antibacterial activity by using agar cup plate method, QSAR will be studied further. The eleven compounds of scheme were subjected to molecular docking studies. The compounds TH1, TH2, TH3, TH4, TH5, TH6, TH8, TH9, TH10 and TH11 showed good negative dock scores. All the N-substituted (tosyl, 4- substituted benzoyl) have shown good negative dock scores with range of -4.3489 to -4.7634. The antimicrobial activity shown by the compounds were less when compared to the standared drugs (ciprofloxacine, fluconazole). The results obtained were statistically analyzed by 3D-QSAR method and found that the PLSR (KNN,MLR) method for 3D-QSAR gave the best results . The predicted values were $r^2 = 0.9977$, $q^2 = 0.0882$, F- test-1709, Pred_ r^2 = -3.309 and Pred_ r^2 se=-1.66. The compounds which are having tosyl have shown good docking scores and potential anti microbial activity (TH1, TH2, TH3, TH4, TH5, TH6, TH11,). The compounds which are having electron donating groups such as methyl on benzoyl nucleus attached to the nitrogen atom of tetrahydrocarbazole have shown good dock scores with good antimicrobial activity.

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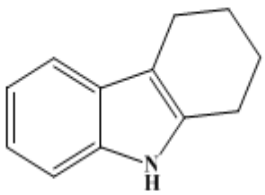
INTRODUCTION

Many compounds containing this heterocycle have pharmaceutical importance. The heterocyclic compound tetrahydrocarbazole and its derivatives are reported to possess varied biological activities.



The recent expansion of antimicrobial drug research has occurred because there is a critical need for new antimicrobial agents to treat these life threatening invasive infections. In modern drug designing, molecular docking is routinely used for understanding drug-receptor interaction.

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The enzyme, namely GlcN-6-P synthase, (L-glutamine: D-fructose-6P amidotransferase), also known under the trivial name of glucosamine-6-phosphate synthase, is a new target for antimicrobials. It is a protein synthesis inhibitor in bacteria. It binds to a small 16s rRNA of the 30s subunit of the bacterial ribosome interfering with the binding of formyl – methionyl - tRNA to the 30s subunit. The molecule tetrahydrocarbazole was reported various activities such as analgesic, anti-inflammatory, antihistaminic, antidepressant, anticancer activities.

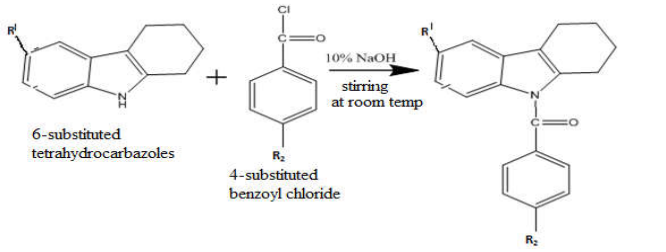
MATERIALS AND METHODS

All the solvents, chemicals and drugs employed for the synthetic work were of SDfine/E.Merck/Loba Laboratory grade. The solvents were purified by the established methods. Few of the reagent materials used in the synthesis were obtained from Sigma Aldrich. All the residues have been dried in vacuum desiccators and recrystallized.

The percentage yields are based upon the products obtained after purification through recrystallization. The IR spectra of compounds were recorded using KBr pellets on FTIR-8400

spectrophotometer Shimadzu make at Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur1H-NMR and 13C spectra (CDCl3 and DMSO) were recorded at SAIF, Punjab University, Chandigarh and SAIF on Bruker Advance-II 400 Spectrometer on 400 MHz and Bruker AVIII on 500 MHz respectively using tetramethylsilane (TMS) as internal standard. The chemical shifts (δ) are reported in parts per million (ppm) relative to TMS in CDCl3 solution. Mass spectra (EIMS) were recorded at Waters, Q-TOF LC-MS spectrometer (Waters, Micromass LC-MS, USA) at Central Instrumentation Laboratory, Punjab University, Chandigarh. Elemental analysis were carried out using FLASH EA 1112 CHN analyzer from Thermo Finnigen, and values within limit of ± 0.4% of the theoretical values

Scheme of the study



Substituted N -(Benzoyl) 1,2,3,4 Tetrhydroacarbazole derivatives

Synthesis of Substituted N -(Benzoyl) 1,2,3,4 Tetrhydrocarbazole derivatives

S.NO	Compound code	IUPAC name	R^1	R^2
1	TH1	(4-chlorophenyl)(6-chloro-1,2,3,4-tetrahydrocarbazol-9-yl)methanone	-C l	-C l
2	TH2	(4-chlorophenyl)(6-fluoro-1,2,3,4-tetrahydrocarbazol-9-yl)methanone	-F	-C l
3	TH3	(4-chlorophenyl)(6-methyl-1,2,3,4-tetrahydrocarbazol-9-yl)methanone	-CH3	-C l
4	TH4	(4-nitrophenyl)(1,2,3,4-tetrahydrocarbazol-9-yl)methanone	-H	-NO2
5	TH5	(6-chloro-1,2,3,4-tetrahydrocarbazol-9-yl)(4-nitrophenyl)methanone	-C l	-NO2
6	TH6	(6-fluoro-1,2,3,4-tetrahydrocarbazol-9-yl)(4-nitrophenyl)methanone	-F	-NO2
7	TH7	(6-methyl-1,2,3,4-tetrahydrocarbazol-9-yl)(4-nitrophenyl)methanone	-CH3	-NO2
8	TH8	(4-methylphenyl)(1,2,3,4-tetrahydrocarbazol-9-yl)methanone	-H	-CH3
9	TH9	(4-methylphenyl)(6-chloro-1,2,3,4-tetrahydrocarbazol-9-yl)methanone	-Cl	-CH3
10	TH10	(4-methylphenyl)(6-fluoro-1,2,3,4-tetrahydrocarbazol-9-yl)methanone	-F	-CH3
11	TH11	(4-methylphenyl)(6-methyl-1,2,3,4-tetrahydrocarbazol-9-yl)methanone	-CH3	-CH3

(4-chlorophenyl)(6-chloro-1,2,3,4-tetrahydro-9H-carbazol-9-yl)methanone(TH1)

Suspended 1gm (0.07 mol) of 6-chlorotetrahydrocarbazole in 20 ml of 10% NaoH solution Into well corked conical flask and add 2ml of 4-chlorobenzoylchloride with constant shaking and cooled in water. Shake vigorously for 10min until the odour of the 4-chlorobenzoylchloride has disappeared. Filtered off the solid (4-chlorophenyl)(6-chloro-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)methanone and washed with a little amount of cold water. Recrystallised from aqueous ethanol.Yield : 55.23 % : mp : 260-262^0 C (Ethanol): R_f : 0.58 (n- hexanol : EtoAC 7:3): IR KBr cm^{-1}:3109.78 (C-H aromatic Stretching) ,2993.01(C-H aliphatic stretching),1748.12 (C=O stretching) ,1615.34 (C=C stretching Ar) ,780.15,736.12 (C-Cl stretching): ^{1}H NMR ($CDCl_3$, 400 MHz) : 2.10 (m, 2H, CH_2) , 2.32 (m, 2H , CH_2) ,3.78(m,4H,CH_2), 6.24 (m. 3H,Ar) , 7.89 (m, 4H, Ar) : ^{13}C NMR ($CDCl_3$,125 MHz) :119.71, 120.89, 121.74, 129.19, 133.84 (Ar), 167.16, 169.19, 171.15 (tetrahydrocarbazole (Ar) , 192 .98 (C=O): Em (Es, Positive mode) m/z 345.34: Anal, Calc for($C_{19}H_{15}Cl_2NO$): C, 66.28; H,4.35; N,4.06: Found: C,66.89; H,4.78; N,4.89.

(4-chlorophenyl)(6-fluoro-1,2,3,4-tetrahydro-9H-carbazol-9-yl)methanone (TH2)

Suspended 1gm (0.07 mol) of 6-fluorotetrahydrocarbazole in 20 ml of 10% NaoH solution Into well corked conical flask and add 2ml of 4-chlorobenzoylchloride with constant shaking and cooled in water. Shake vigorously for 10min until the odour of the 4-chlorobenzoylchloride has disappeared. Filtered off the solid (4-chlorophenyl)(6-fluoro-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)methanone and washed with a little amount of cold water. Recrystallised from aqueous ethanol.Yield : 59.67 % : mp : 264-266^0 C (Ethanol): R_f : 0.60 (n- hexanol : EtoAC 7:3): IR KBr cm^{-1}:3111.18 (C-H aromatic Stretching) ,2943.37(C-H aliphatic stretching),1729.65 (C=O stretching) ,1615.36 (C=C stretching Ar) ,1130.29 (C-F stretching),745.23 (C-Cl stretching): ^{1}H NMR ($CDCl_3$, 400 MHz) : 2.08 (m, 2H, CH_2) , 2.32 (m, 2H , CH_2), 2.86(m,4H, CH_2), 6.24 (m. 3H,Ar) , 7.89 (m, 4H, Ar) : ^{13}C NMR ($CDCl_3$,125 MHz) :119.78, 120.84, 121.754, 129.23, 133.67 (Ar), 167.45, 169.87, 171.23 (tetrahydrocarbazole (Ar) , 192 .13 (C=O): Em (Es, Positive mode) m/z 328.45: Anal, Calc for($C_{19}H_{15}ClFNO$): C, 69.61; H,5.49; N,4.32: Found: C,69.78; H,5.89; N,4.69.

(4-chlorophenyl)(6-methyl-1,2,3,4-tetrahydro-9H-carbazol-9-yl)methanone (TH3)

Suspended 1gm (0.07 mol) of 6-methyltetrahydrocarbazole in 20 ml of 10% NaoH solution Into well corked conical flask and add 2ml of 4-chlorobenzoylchloride with constant shaking and cooled in water. Shake vigorously for 10min until the odour of the 4-chlorobenzoylchloride has disappeared. Filtered off the solid (4-chlorophenyl)(6-methyl-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)methanone and washed with a little amount of cold water. Recrystallised from aqueous ethanol.Yield : 54.78 % : mp : 272-274^0 C (Ethanol): R_f : 0.59 (n- hexanol : EtoAC 7:3): IR KBr cm^{-1}:3052.41 (C-H aromatic Stretching) ,2927.56(C-H aliphatic stretching),1742.56 (C=O stretching) ,1617.98 (C=C stretching Ar),1423.56 (C-CH_3 stretching),765.23 (C-Cl stretching): ^{1}H NMR ($CDCl_3$, 400 MHz) : 2.45 (m, 2H, CH_2) , 2.57 (m, 2H , CH_2) ,2.89(m,4H, CH_2), 6.16 (m. 3H,Ar) , 7.45 (m, 4H, Ar) : ^{13}C NMR ($CDCl_3$,125 MHz) :119.68, 120.48, 121.28, 129.89, 133.689 (Ar), 167.29, 169.20, 171.219 (tetrahydrocarbazole (Ar) , 192 .78 (C=O): Em (Es, Positive mode) m/z 324.89: Anal, Calc for($C_{20}H_{18}NClO$): C, 74.17; H,5.55; N,4.31: Found: C,75.89; H,5.78; N,4.79.

(4-nitrophenyl)(1,2,3,4-tetrahydro-9H-carbazol-9-yl)methanone (TH4)

Suspended 1gm (0.07 mol) of tetrahydrocarbazole in 20 ml of 10% NaoH solution Into well corked conical flask and add 2ml of 4-nitrobenzoylchloride with constant shaking and cooled in water. Shake vigorously for 10min until the odour of the 4-nitrobenzoylchloride has disappeared. Filtered off the solid (4-nitrophenyl)(1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)methanone and washed with a little amount of cold water. Recrystallised from aqueous ethanol. Yield : 59.34 % : mp : 262-264^0 C

(Ethanol): R_f : 0.63 (n- hexanol : EtoAC 7:3): IR KBr cm^{-1}:3125.78 (C-H aromatic Stretching) ,2987.45(C-H aliphatic stretching),1702.78 (C=O stretching) ,1635.78 (C=C stretching Ar) ,1226.78 (C-NO_2 stretching),765.23 : ^{1}H NMR ($CDCl_3$, 400 MHz) : 2.35 (m, 2H, CH_2) , 2.45 (m, 2H , CH_2) ,2.79(m,4H, CH_2), 6.54 (m. 3H,Ar) , 7.79 (m, 4H, Ar) : ^{13}C NMR ($CDCl_3$,125 MHz) :119.23, 120.89, 121.45, 129.14, 133.78 (Ar), 167.58, 169.34, 171.29 (tetrahydrocarbazole (Ar) , 192 .68 (C=O): Em (Es, Positive mode) m/z 321.341: Anal, Calc for(C_{19} H_{16} N_2O_3): C, 71.12; H,4.99; N,8.74: Found: C,72,67; H,5,12; N,8,92.

(6-chloro-1,2,3,4-tetrahydro-9H-carbazol-9-yl)(4-nitrophenyl)methanone (TH5)

Suspended 1gm (0.07 mol) of 6-chlorotetrahydrocarbazole in 20 ml of 10% NaoH solution Into well corked conical flask and add 2ml of 4-nitrobenzoylchloride with constant shaking and cooled in water. Shake vigorously for 10min until the odour of the 4-nitrobenzoylchloride has disappeared. Filtered off the solid (4-nitrophenyl)(6-chloro-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)methanone and washed with a little amount of cold water. Recrystallised from aqueous ethanol.Yield : 60.15 % : mp : 278-280^0 C (Ethanol): R_f : 0.76 (n- hexanol : EtoAC 7:3): IR KBr cm^{-1}:3167.45 (C-H aromatic Stretching) ,2978.56(C-H aliphatic stretching),1726.89 (C=O stretching) ,1660.57 (C=C stretching Ar) ,1356.23 (C-NO_2 stretching),756.46 (C-Cl stretching) : ^{1}H NMR ($CDCl_3$, 400 MHz) : 2.56 (m, 2H, CH_2) , 2.78 (m, 2H , CH_2) ,2.89(m,4H, CH_2), 6.54 (m. 3H,Ar) , 7.16 (m, 4H, Ar) : ^{13}C NMR ($CDCl_3$,125 MHz) :119.18, 120.78, 121.24, 129.78, 133.94 (Ar), 167.25, 169.67, 171.79 (tetrahydrocarbazole (Ar) , 192 .74 (C=O): Em (Es, Positive mode) m/z 355.68s: Anal, Calc for(C_{19} H_{15}Cl N_2O_3): C, 64.31; H,4.22; N,7.89: Found: C,65.34; H,4.89; N,7.43.

(6-fluoro-1,2,3,4-tetrahydro-9H-carbazol-9-yl)(4-nitrophenyl)methanone (TH6)

Suspended 1gm (0.07 mol) of 6-flurotetrahydrocarbazole in 20 ml of 10% NaoH solution Into well corked conical flask and add 2ml of 4-nitrobenzoylchloride with constant shaking and cooled in water. Shake vigorously for 10min until the odour of the 4-nitrobenzoylchloride has disappeared. Filtered off the solid (4-nitrophenyl)(6-fluro-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)methanone and washed with a little amount of cold water.Yield : 54.98 % : mp : 280-282^0 C (Ethanol): R_f : 0.78 (n- hexanol : EtoAC 7:3): IR KBr cm^{-1}:3121.89 (C-H aromatic Stretching) ,2987.47(C-H aliphatic stretching),1710.14 (C=O stretching) ,1635.76 (C=C stretching Ar) ,1335.67 (C-NO_2 stretching),746.35 (C-Cl stretching) : ^{1}H NMR ($CDCl_3$, 400 MHz) : 2.34 (m, 2H, CH_2) , 2.57 (m, 2H , CH_2) ,2.92(m,4H, CH_2), 6.16 (m. 3H,Ar) , 7.27 (m, 4H, Ar) : ^{13}C NMR ($CDCl_3$,125 MHz) :119.19, 120.28, 121.24, 129.39, 133.29 (Ar), 167.36, 169.28, 171.98 (tetrahydrocarbazole (Ar) , 192 .89 (C=O): Em (Es, Positive mode) m/z 339.45: Anal, Calc for(C_{19} H_{15}F N_2O_3): C, 67.44; H,4.43; N,8.27: Found: C,67.34; H,4.80; N,8.49.

(6-nitro-1,2,3,4-tetrahydro-9H-carbazol-9-yl)(4-nitrophenyl)methanone (TH7)

Suspended 1gm (0.07 mol) of 6-nitrotetrahydrocarbazole in 20 ml of 10% NaoH solution Into well corked conical flask and add 2ml of 4-nitrobenzoylchloride with constant shaking and cooled in water. Shake vigorously for 10min until the odour of the 4-nitrobenzoylchloride has disappeared. Filtered off the solid (4-nitrophenyl)(6-nitro-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)methanone and washed with a little amount of cold water. Recrystallised from aqueous ethanol.Yield : 57.45 % : mp : 282-284^0 C (Ethanol): R_f : 0.80 (n- hexanol : EtoAC 7:3): IR KBr cm^{-1}:3135.35 (C-H aromatic Stretching) ,2927.46(C-H aliphatic stretching),1708.34 (C=O stretching) ,1618.34 (C=C stretching Ar) ,1435.24,1337.89. (C-NO_2 stretching),746.35 : ^{1}H NMR ($CDCl_3$, 400 MHz) : 2.16 (m, 2H, CH_2) , 2.35 (m, 2H , CH_2) ,2.39(m,4H, CH_2), 6.25 (m. 3H,Ar) , 7.78 (m, 4H, Ar) : ^{13}C NMR ($CDCl_3$,125 MHz) :119.89, 120.57, 121.45, 129.47, 133.69 (Ar), 167.37, 169.69, 171.35 (tetrahydrocarbazole (Ar) , 192 .25 (C=O): Em (Es, Positive mode) m/z 366.89: Anal, Calc for(C_{19} H_{15} N_3O_5): C, 62.46; H,4.10; N,11.49: Found: C,63.67; H,4.56; N,11.78.

(4-methylphenyl)(1,2,3,4-tetrahydro-9H-carbazol-9-yl)methanone (TH8)

Suspended 1gm (0.07 mol) of tetrahydrocarbazole in 20 ml of 10% NaoH solution Into well corked conical flask and add 2ml of 4-methylbenzoylchloride with constant shaking and cooled in water. Shake vigorously for 10min until the odour of the 4-methylbenzoylchloride has disappeared. Filtered off the solid (4-methylphenyl)(1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)methanone and washed with a little amount of cold water. Recrystallised from aqueous ethanol.Yield : 53.78 % : mp : 283-285^0 C (Ethanol): R_f : 0.82 (n- hexanol : EtoAC 7:3): IR KBr cm^{-1}:3094.88 (C-H aromatic Stretching) ,2987.45(C-H aliphatic stretching),1702.67 (C=O stretching) ,1657.34 (C=C stretching Ar) ,1342 (C-CH_3 stretching) : ^{1}H NMR ($CDCl_3$, 400 MHz) :1.96(m.3H, CH_3) , 2.46 (m, 2H, CH_2) , 2.56 (m, 2H , CH_2) ,2.78 (m,4H, CH_2), 6.34 (m. 4H,Ar) , 7.36 (m, 4H, Ar) : ^{13}C NMR ($CDCl_3$,125 MHz) :119.34, 120.68, 121.35, 129.89, 133.46 (Ar), 167.57, 169.89, 171.36 (tetrahydrocarbazole (Ar) , 192 .49 (C=O): Em (Es, Positive mode) m/z 290.57: Anal, Calc for(C_{20} H_{19} NO): C, 83.00; H,6.56; N,4.83: Found: C,83.56; H6.89; N,4.78.

(4-methylphenyl)(6-chloro-1,2,3,4-tetrahydro-9H-carbazol-9-yl)methanone (TH9)

Suspended 1gm (0.07 mol) of 6-chlorotetrahydrocarbazole in 20 ml of 10% NaoH solution into well corked conical flask and add 2ml of 4-methylbenzoylchloride with constant shaking and cooled in water. Shake vigorously for 10min until the odour of the 4-methylbenzoylchloride has disappeared. Filtered off the solid (4-methylphenyl)(6-chloro-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)methanone and washed with a little amount of cold water. Recrystallised from aqueous ethanol.Yield : 58.97 % : mp : 287-289^0 C (Ethanol): R_f : 0.91 (n- hexanol : EtoAC 7:3): IR KBr cm^{-1}:3089.45 (C-H aromatic Stretching) ,2967.46(C-H aliphatic stretching),1703.39 (C=O stretching) ,1606.25 (C=C stretching Ar) ,1236.78 (C-CH_3 stretching),675.32 (C-Cl stretching) : ^{1}H NMR ($CDCl_3$, 400 MHz) :1.86(m.3H, CH_3) , 2.51 (m, 2H, CH_2) , 2.48 (m, 2H , CH_2) ,2.65 (m,4H, CH_2), 6.32 (m. 3H,Ar) , 7.34 (m, 4H, Ar) : ^{13}C NMR ($CDCl_3$,125 MHz) :118.24, 119.66, 120.45, 134.86, 135.57 (Ar), 168.42, 169.65, 170.34 (tetrahydrocarbazole (Ar) , 193 .58 (C=O): Em (Es, Positive mode) m/z 323.18: Anal, Calc for(C_{20} H_{18}Cl NO): C, 74.32; H,5.56; N,4.33: Found: C,75.66; H5.90; N,4.33.

(4-methylphenyl)(6-fluoro-1,2,3,4-tetrahydro-9H-carbazol-9-yl)methanone (TH10)

Suspended 1gm (0.07 mol) of 6-fluorotetrahydrocarbazole in 20 ml of 10% NaoH solution into well corked conical flask and add 2ml of 4-methylbenzoylchloride with constant shaking and cooled in water. Shake vigorously for 10min until the odour of the 4-methylbenzoylchloride has disappeared. Filtered off the solid (4-methylphenyl)(6-fluoro-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)methanone and washed with a little amount of cold water. Recrystallised from aqueous ethanol.Yield : 68.43 % : mp : 297-299^0 C (Ethanol): R_f : 0.96 (n- hexanol : EtoAC 7:3): IR KBr cm^{-1}:2987.67 (C-H aromatic Stretching) ,2856.34(C-H aliphatic stretching),1745.67 (C=O stretching) ,1610.45 (C=C stretching Ar) ,1345.89 (C-CH_3 stretching),1135.89(C-F stretching) : ^{1}H NMR ($CDCl_3$, 400 MHz) :1.67(m.3H, CH_3) , 2.46 (m, 2H, CH_2) , 2.56 (m, 2H , CH_2) ,2.72 (m,4H, CH_2), 6.89 (m. 3H,Ar) , 7.12 (m, 4H, Ar) : ^{13}C NMR ($CDCl_3$,125 MHz) :117.12, 118.76, 119.13., 132.89,
138.24 (Ar), 167.35, 168.23, 169.48 (tetrahydrocarbazole (Ar) , 194 .56 (C=O): Em (Es, Positive mode) m/z 308.89: Anal, Calc for(C_{20} H_{18}F NO): C, 78.32; H,5.85; N,4.55: Found: C,79.65; H,5.34; N,4.68.

(4-methylphenyl)(6-methyl-1,2,3,4-tetrahydro-9H-carbazol-9-yl)methanone (TH11)

Suspended 1gm (0.07 mol) of 6-methyltetrahydrocarbazole in 20 ml of 10% NaoH solution into well corked conical flask and add 2ml of 4-methylbenzoylchloride with constant shaking and cooled in water. Shake vigorously for 10min until the odour of the 4-methylbenzoylchloride has disappeared. Filtered off the solid (4-methylphenyl)(6-methyl-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)methanone and washed with a little amount of cold water. Recrystallised from aqueous ethanol.Yield : 63.38 % : mp : 302-304^0 C (Ethanol): R_f : 0.12 (n- hexanol : EtoAC 7:3): IR KBr cm^{-1}:3021.78 (C-H aromatic Stretching) ,2976.46(C-H aliphatic stretching),1708.38 (C=O stretching) ,1598.56 (C=C stretching Ar) ,1240.67 (C-CH_3 stretching),1156.78(C-Cl stretching) : ^{1}H NMR ($CDCl_3$, 400 MHz) :1.72(m.3H, CH_3) , 2.34 (m,3H, CH_3), 2.89 (m, 2H, CH_2) , 2.92 (m, 2H , CH_2) ,3.12 (m,4H, CH_2), 6.87 (m. 3H,Ar) , 7.14 (m, 4H, Ar) : ^{13}C NMR ($CDCl_3$,125 MHz) :118.14,
119.56, 123.18., 134.91, 137.41 (Ar), 168,56., 169.78, 170.69 (tetrahydrocarbazole (Ar) , 195 .34 (C=O): Em (Es, Positive mode) m/z 304.69: Anal, Calc for(C_{21} H_{21} NO): C, 83.12; H,6.92; N,4.61: Found: C,84.78; H,7.89; N,4.75.

Molecular docking studies (1XFF)

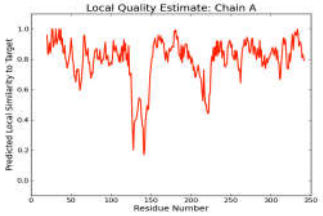
The homology modelling was carried out by Vlife MDS and Swiss-Model software, the receptor for molecular docking of compounds from schemes was selected on the basis of literature, Ciprofloxacine, flucanazole were used as the standard drug for this study. The FASTA format for sequence of amino acids were obtained from Protein Data Bank (PDB) with Id:1XFF and submitted for building the model, alternatively the crystal structure was obtained from the same site and refined in VLife module. Models were built based on the target template alignment using ProMod-II. Coordinates which are conserved between the target and the template were copied from the template to the model. Insertions and deletions were remodelled using a fragment library. Side chains were then rebuilt. Finally, the geometry of the resulting model was regularized by using a force field. In case loop modelling with ProMod-II (Guex, *et al*., 1997) does not give satisfactory results, an alternative model was built with MODELLER (Sali, *et al*., 1993). The global and per-residue model quality was assessed using the QMEAN scoring function (Benkert, *et al*., 2011). For improved performance, weights of the individual QMEAN terms have been trained specifically for SWISS-MODEL. Both the models from Swiss-Model and Vlife were analysed on the basis of Ramchandran plot, both had similar placement of amino acids as can be seen from the Qmean plot

Homology modeling of L-Glutamine D-Fructose-6-Phosphate amido transferase (1XFF)

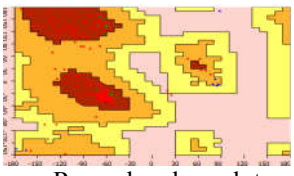
Amino acid sequence for 1XFF in

```
>1T0J:A|PDBID|CHAIN|SEQUENCE
GHMGSADSYTSRPSDSDVSLEEDREAVRREAERQAQAQLEKAKTKPVAFAVRTNVRYSAAQE
DDVPVPGMAISFEAKDFLHVKEKFNNDWWIGRLVKEGCEIGFIPSPVKLENMRLQHEQRAKQ
GKFYSSKS
>1T0J:B|PDBID|CHAIN|SEQUENCE
MSKEKRMPFFKKTEHTPPYDVVPSMRPVVLVGPSLKGYEVTDMMQKALFDFLKHRFEGRISI
TRVTADISLAKRSVLNNPSKHAIIERSNTRSSLAEVQSEIERIFELARTLQLVVLDADTINH
PAQLSKTSLAPIIVYVKISSPKVLQRLIKSRGKSQAKHLNVQMVAADKLAQCPPQESFDVIL
DENQLEDACEHLADYLEAYWKATHPPSSNLPNPLLSRT
```

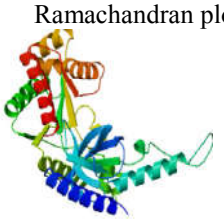
FASTA format



Qmean plot



Ramachandran plot



Protein model

Ramachandran plot

Q mean plot obtained for similarity search using similar template and formation of structural model

Preparation of ligands for molecular docking

A library of compounds with basic nucleus consisting of substituted tetrahydrocarbazoles derivatives was constructed with help of ChemSketch software and ligands were optimised from 2D to 3D in Vlife softwar

Molecular docking for L-Glutamine D-Fructose-6-Phosphate amido transferase (1XFF) for substituted tetrahydrocarbazoles

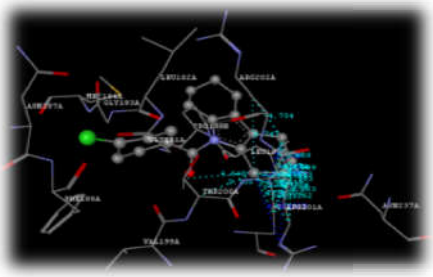
The receptor and ligands were subjected to molecular docking employing the 'Biopredicta' module of VLife software. The docking protocol in Biopredicta runs on genetic algorithm

(GA-based) which approximates a systematic search of positions, orientations and conformations of the ligand in the receptor binding pocket. The dock score is affected by various input parameters such as Number of cycles, Rotation limits, Translation, Convergance, Flexibility of receptor and igands. The compounds with comparatively good dock score, hydrophobic, charged and van der Waals (vdW) interactions as shown in **table.** The molecular interaction and pictorial presentation in 2D and 3D form is given in figure. , the library was screened to limit the compounds to 11 numbers for purpose of synthesis and subsequent pharmacological screening.

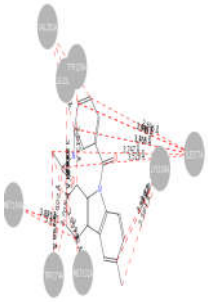
Results of molecular docking for 1XFF with ligands

s.no	Ligand	Docking scores	*Hydrogen bond*	*Hydrophobic interactions*	*charge*	*Pi-staking*	*vdw*
1	TH1	-4.3678	1	7	1	1	11
2	TH2	-4.6489	1	13	1	1	16
3	TH3	--4.1489	1	8	1	1	13
4	TH4	-4.9854	1	21	1	1	23
5	TH5	-4.6432	1	19	4	1	13
6	TH6	-4.9654	1	17	3	1	21
7	TH7	-o.6732	1	19	1	1	35
8	TH8	-4.9245	1	18	4	1	22
9	TH9	0.9456	1	35	2	1	45
10	TH10	-4.7632	1	-	5	1	22
11	TH11	-4.9542	1	22	4	1	53
12	Ciprofloxacine	-4.5399	1	36	4	1	58
13	fluconazole	-4.9567	1	48	4	1	62

Docked complex of TH3 with 1XFF



DockedComplex of TH-9 with 1XFF



2D Grphical representation

3D-QSAR studies (Anti-microbial activity)

A Quantitative Structure Activity Relationship (QSAR) is a study of the dependence upon chemical structure of some observable property or 'activity' over a collection of chemical compounds. Modelling this dependence enables predictions to be made about the activity of synthesised compounds and hints for the design of new and better Molecules.

Data set and biological activity

The results obtained from anti-microbial activity were employed for carrying out the 3D-QSAR studies, the ED50 values of eleven compounds employed to obtain the statistical analysis on basis of various descriptors such as steric, electrostatic and hydrophobic which were calculated and used as independent variables .

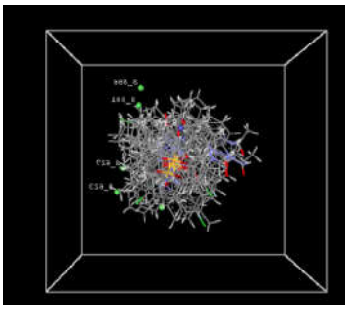
Selection of training and test set

The dataset of 11 molecules was divided into training and test set by random selection method for MLR, PCR, PLSR and kNN-MFA model. The percentage selection criteria were used for dividing test and training set (in between 60% to 85%).

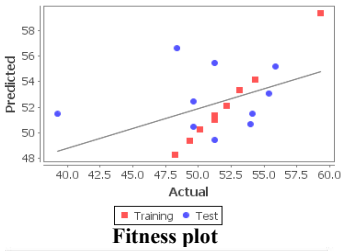
S,NO	Method	r^2	q^2	F-test	pred_ r^2	Pred_ r^2se
1	MLR	o.9981	0.9800	527.606	-2.9246	0.0958
2	PLSR	0.9977	0.0882	1709.37	--3.3755	1.6625
3	PCR	0.8307	-0.0365	19.621	-2.4377	0.7164
4	KNN	-	0.5128	-	-0.2794	-

METHODOLOGY

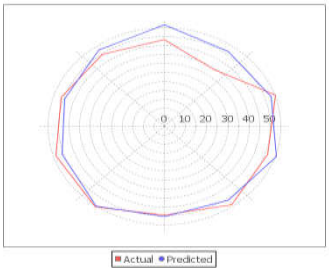
Comparative results of 3D-QSAR methods



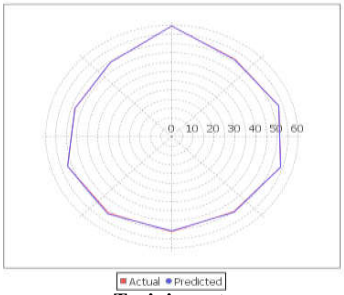
3D Representation



Fitness plot



Test set

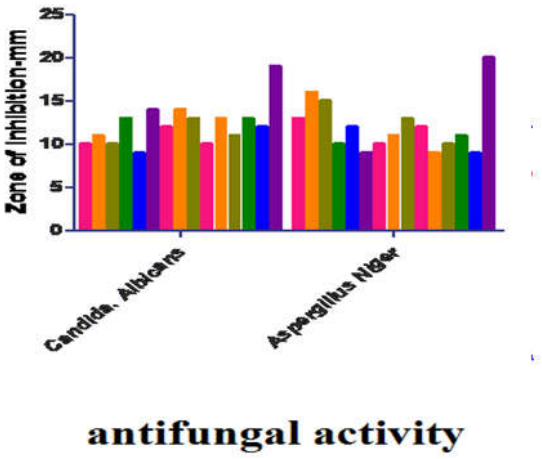


Training set

Anti-bacterial activity

Determination by Agar cup method

The antibacterial activity of 1,2,3,4-tetrahydrocarba-zolederivatives was studied by agar cup method. The nutrient broth culture media was chosen as basal medium for testing the microbe. The nutrient broth medium (Hi media M0001) was plated into Petri dishes, allowed to solidification and then the microbe was inoculated into broth medium and allowed for incubation for a period of 24 hours at 25°C. Bacterial culture was spread evenly over the entire surface to avoid the aggregation and left undisturbed for few minutes to permeate the culture. The wells/ holes (4 mm) were drawn using a sterile borer into the solidified nutrient medium. The compounds of substituted tetrahydrocarbazoles were added to each well (100µL) at peripheral of the petridish and the reference compounds (ciprofloxacin for bacterial, fluconazole for fungal) was added at the centre and then the plates are incubated for 24hrs at 25°C. The plates were collected and analyze the zone of inhibition with respect to millimeters (mm). DMSO is used as a control.



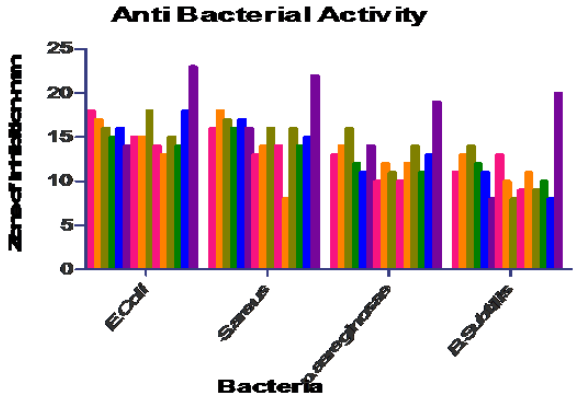
antifungal activity

Zone of Inhibition

S.NO	Ligands	E.Coli ATCC 25922	S.areus ATCC29213	p.aereginosae ATCC27953	B.Subtilis ATCC6633	Candida. Albicans NRCC2477	Aspergillus Niger
1	TH1	16	15	12	12	11	12
2	TH2	16	17	15	14	12	15
3	TH3	15	16	13	13	11	14
4	TH4	14	15	11	13	14	11
5	TH5	15	16	12	12	8	11
6	TH6	13	14	11	9	11	8
7	TH7	13	12	11	12	11	11
8	TH8	12	11	13	11	12	10
9	TH9	16	14	12	8	12	11
10	TH10	16	11	10	9	11	10
11	TH11	14	12	10	9	8	10
12	CIPRO	23	22	19	20		
13	FLUCANAZOLE					19	20

Minimum inhibitory concentrations (µg)

S.NO	Ligands	E.Coli ATCC 25922	S.areus ATCC29213	p.aereginosae ATCC27953	B.Subtilis ATCC6633	Candida. Albicans NRCC2477	Aspergillus Niger
1	TH1	25	50	50	100	100	100
2	TH2	50	25	25	25	100	75
3	TH3	25	75	75	50	75	50
4	TH4	50	100	50	100	100	100
5	TH5	100	50	50	50	75	75
6	TH6	75	50	75	75	100	50
7	TH7	50	100	50	100	75	75
8	TH8	50	25	100	75	50	100
9	TH9	25	50	50	75	75	100
10	TH10	100	100	75	50	100	75
11	TH11	25	50	100	75	75	100
12	CIPRO	25	25	25	25		
13	FLUCANAZOLE					25	25



RESULTS AND DISCUSSION

The compounds of scheme were synthesized by mixing and stirring the 6-substituted tetrahydrocarbazoles with the 4-substituted benzoyl chloride in 10% NaOH. The purified compounds were subjected to CHN analysis. The results obtained were correlated with the calculated values and were in close agreement. IR spectra of the compounds showed characteristic carbonyl peak in the region of 1715.26cm $^{-1}$ and the remaining halogen peaks at respective position. ^{1}H NMR showed the δ values for aliphatic protons's in the regions of δ2.12-2.90. and aromatic protons δ6.73-7.36. All the compounds showed characteristic molecular ionic peaks at m/z.

Later all the 11 compounds were subjected to molecular docking studies to know the interactions between the molecules and the receptors. They were subjected to antimicrobial activity. The obtained antimicrobial activity data was incorporated into two way anova studies. The results are represented in the graphical form.

The animal activity data was subjected to QSAR studies. A Quantitative Structure Activity Relationship (QSAR) is a study of the dependence upon chemical structure of some observable property or 'activity' over a collection of chemical compounds. This enables predictions to be made about the activity of synthesised compounds and hints for the design of new and better molecules. Compounds were employed to obtain the statistical analysis on basis of various descriptors such as steric, electrostatic and hydrophobic interaction which were calculated and used as independent variables.

The dataset of molecules was divided into training and test set by random selection method for MLR, PCR, PLSR and kNN-MFA model. The percentage selection criteria were used for dividing test and training set (in between 60% to 85%). The statistical data was generated which results in coefficient of determination (r2), cross validated coefficient of determination (q2), r2 for external test set (pred_r2) fitness plot and points of distribution. The result of 3D QSAR is presented in the figures in the QSAR**,** that presents the distribution plot for test and the data set, the contribution plot for various descriptors, for various training sets. The data set for 3D QSAR analysis with actual and predicted IC50 values of compounds are mentioned. All the molecules showed good predictability.

CONCLUSION

The homology modeling was carried out by V life MDS softwear. The enzyme L-Glutamine. D-fructose-6-phosphate amino transferase [Glcn-6-p]-code 1XFF was selected for Molecular docking studies. It has nine active pockets in which the second cavity have shown the good activity. The FASTA format of the sequence for amnio acids was obtained from protein Data bank (PDB) Id: 1XFF.

The 11 compounds of Scheme were subjected to molecular docking studies. The compounds TH1, TH2, TH3, TH4, TH5, TH6, TH8, TH9, TH10 and TH11 showed good negative dock scores. The compounds showed hydrogen bond with the amino acids Cys135A, Gly136A, and Asp138A. The compounds showed hydrophobic, charge, Pi-staking and vdw interactions with the amino acids Leu150A, Asp162A, Gly164, Val72A, Ala176A and Ilc178A. All the N-substituted (tosyl, 4-substituted benzoyl) have shown good negative dock scores with range of -4.3489 to -4.7634.

The compounds have shown good zone of inhibition when they were subjected to agar cup plate method. The compounds were studied to know the zone of inhibition**.** It can be concluded that the presence of polar groups (benzoyl, tosylgroups) attached to nitrogen of the tetrahydrocarbozole affect the anti-microbial activity. The compounds were subjected for the evaluation of zone of inhibition. MIC was 25µg which was shown by the compounds –TH1, TH3, TH9, TH11 for E.coli, TH-2, TH8, for S.aureus, TH-2, P.aruginosa, TH2 for B.subtilis, 75µg for TH2 for C. albicans, TH-2, TH5, TH7, TH10 for A.niger. The antimicrobial activity shown by the compounds were less when compared to the standared drugs (ciprofloxacine, flucanazole).

The results of antimicrobial activity was analysed by anova studies. The test compounds showed high potent activity against gramme positive bacteria compared to the gramme negative bacteria. Minimum inhibitory concentrations are also measured they shown moderate activity.The antifungal activity was moderate to high but when compared to the standared it was less.

The results obtained were statistically analyzed by 3D-QSAR method and found that the PLSR (KNN,MLR) method for 3D-QSAR gave the best results. The predicted values were r^2 = 0.9977, q^2 = 0.0882, F- test- 1709, Pred_ r^2 = -3.309 and Pred_ r^2 se=-1.66. The fitness plot showed a linear distribution of the test and training set which is supported by the diagrammatic representation of training set and test set analysis by the QSAR method as presented in figures.

The contribution plot and 3D – QSAR graphical interface provide with the point generated in the model were E_143, H_87, S_193 accounting for electrostatic, hydrophobic, and steric fields at the lattice points on the grid. These points suggest the significance and requirements of the these properties in the structure to maximize the anti-microbial activity. There is less significant difference in the actual and predicted activity that provides with good predictive ability of the QSAR tool model**.** This can be observed from the fitness plot.

The contribution plot and 3D – QSAR graphical interface provide with the point generated in the model were E_ 223, H_118, S_224 accounting for electrostatic, hydrophobic, and stearic fields at the lattice points on the grid. These points suggest the significance and requirements of the these properties in the structure to maximize the anti-microbial Activity.

The compounds which are having tosyl have shown good docking scores and potential anti microbial activity (TH1,TH2,TH3, TH4, TH5, TH11,). The compounds which are having electron donating groups such as methyl on benzoyl nucleus attached to the nitrogen atom of tetrahydrocarbazole have shown good dock scores with good antimicrobial activity.

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